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THE ATELECTATIC COMPLEX OF THE LEFT LUNG

by

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The condition known as lamellary atelectasis was first described by HULTÉN (1928) in association with pancreatitis. Later it was also observed, for example, in adipose and recumbent patients with deficient diaphragmatic ventilation. Its cause was generally believed to be processes below the diaphragm although the mechanism underlying this type of atelectasis may also be intrathoracic processes, as described by FLEISCHNER (1936) and STRNAD (1942). HAUBRICHT (1953) believed lamellary atelectasis in the lower lobe to arise from the downward displacement of the lung 'joints' (normally situated in the interlobar spaces) when diaphragmatic respiration diminishes in relation to costal respiration. In those parts of the pulmonary parenchyma where ventilation has become inadequate, the retention of mucous material causes lamellary atelectasis.

HAUBRICHT's theory probably accounts for the genesis of most of the lamellary atelectases. We have, however, noted that lamellary atelectasis may also coexist with ordinary atelectasis of the lower lobe. This combination of two different types of atelectasis has hitherto been observed only on the left side, a predilection which cannot be explained by the reduction in the ventilatory function of the diaphragm.

Lamellary atelectasis usually affects the lingula of the left lung and is combined with atelectasis of the lower lobe. The reduction in the lung

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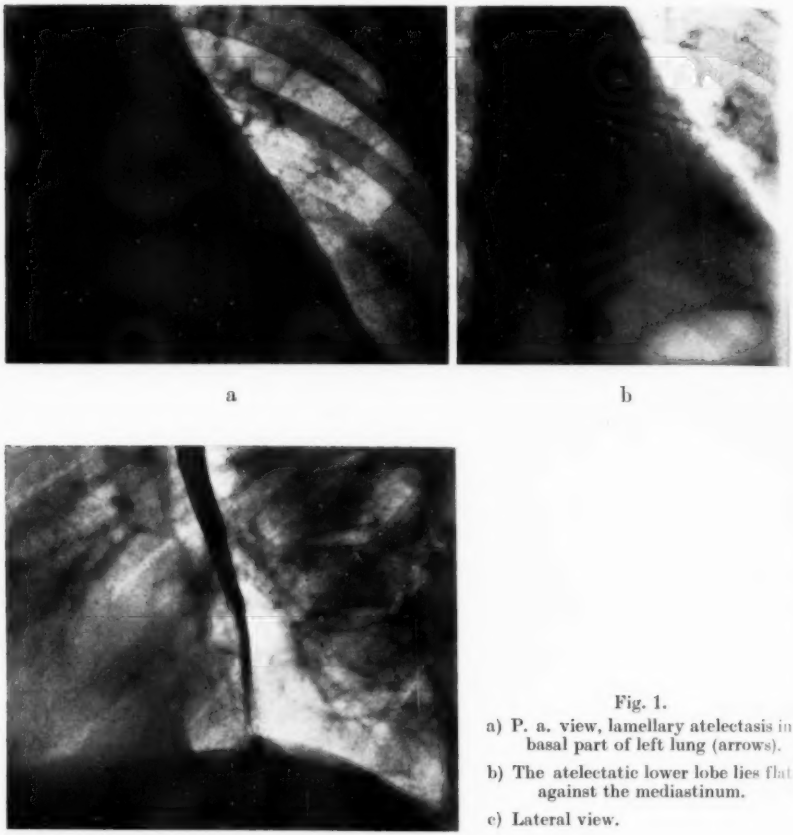

Fig. 1.
a) P. a. view, lamellary atelectasis in basal part of left lung (arrows).
b) The atelectatic lower lobe lies flat against the mediastinum.
c) Lateral view.

volume by the lower lobe atelectasis causes displacement of the lower portion of the mediastinum to the left. Compensatory emphysema develops in the upper lobe which is rotated anteriorly and downwards, and the bronchi and parenchyma of the lower part of the lingula are then kinked against the somewhat elevated diaphragm. This kinking will lead to the development in this part of the lung of lamellary atelectases which are generally demonstrable in the basal peripheral zones. They are secondary to a more important primary atelectasis of the lower lobe which may be more difficult to detect than the lesser lamellary lesions.

In Fig. 1 an example of this type of lamellary atelectasis is shown in a case of bronchial adenoma of carcinoid type occluding the lower lobe

Fig. 2. Bronchography of the same patient as in fig. 1. Atelectatic lower lobe, distal portions of bronchi of lingula kinked against the diaphragm.

bronchus. The patient has had recurrent left pleuro-pneumonia for the previous 18 months. The lamellary atelectasis is seen in the p. a. view laterally to the left margin of the heart. Compensatory emphysema is present in the upper lobe. Lower lobe atelectasis is usually well shown in frontal views when the heart is adequately penetrated (Fig. 1b). Generally, however, it is more easily demonstrable when the patient is turned 45 degrees to the left. The lower part of the mediastinum is slightly displaced to the left. Fig. 1c shows that the collapsed lower lobe may sometimes be rather difficult to identify in lateral projections when it lies flat against the mediastinum. In Fig. 2 films from bronchography of the left lung of the

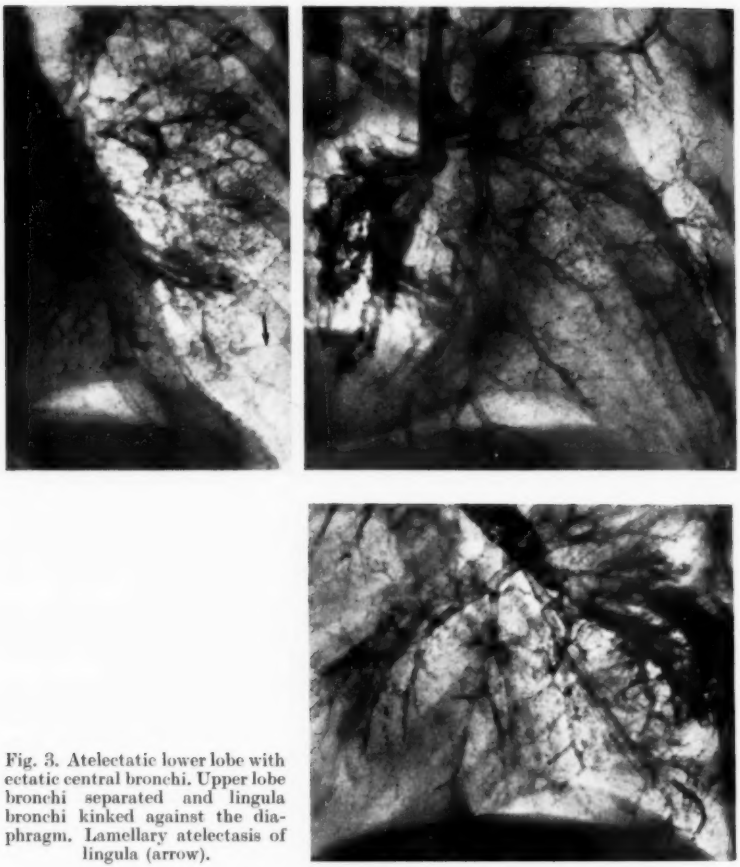

Fig. 3. Atelectatic lower lobe with ectatic central bronchi. Upper lobe bronchi separated and lingula bronchi kinked against the diaphragm. Lamellary atelectasis of lingula (arrow).

same patient are shown. The basal segments of the lower lobe are atelectatic and the bronchi of the upper lobe are separated. The whole upper lobe has an increased volume and is rotated anteriorly and downwards. The distal parts of the lingula bronchi are kinked against the somewhat elevated diaphragm.

Fig. 3 is another example of the kinking of the bronchi in the lingula lobe, represented by a 66-year-old male, having had pulmonary tuberculosis 36 years earlier, and frequent periods of fever, cough and expectoration during the previous 8 months. Almost the whole lower lobe is atelectatic. The distended upper lobe has rotated anteriorly and do wn-

Fig. 4. Atelectatic lower lobe is seen to the right of the heart in the upper view. No lamellary atelectasis. The bronchogram, right lower view, shows that the lower lobe bronchus is occluded by a tumour. The bronchi in the nonatelectatic portion of the lung have a straight course.

wards and the lingula is kinked against the diaphragm. Lamellary atelectasis is present in the basal portion of the left lung.

Fig. 4 shows a tumour wholly occluding the bronchus of the right lower lobe. The films are from a 59-year-old male, who during the preceding year had had cough and expectoration. Despite the total atelectasis

of the lower lobe, the middle lobe bronchi are not kinked against the right cupola of the diaphragm, and no secondary lamellary atelectasis is evident. The primary atelectasis of the lower lobe is seen clearly in the frontal view just to the right of the heart; in the lateral view the atelectasis is more difficult to detect.

Discussion

The mechanism underlying lamellary atelectasis of the lingula would appear to be as follows. Atelectasis of the left lower lobe develops first and constitutes a 'primary' atelectasis caused by obstruction of the lower lobe bronchus. The reduction in the volume of the lower lobe leads to compensatory emphysema of the upper lobe. The left cupola of the diaphragm, normally more mobile than the right, is turned upwards and the mediastinum drawn over somewhat to the left. In addition to the expansion of the upper lobe and the elevation of the left cupola of the diaphragm, the upper lobe also rotates anteriorly and downwards; the peripheral bronchi of the lingula will then be kinked against the left cupola of the diaphragm. The ventilation of the lung distal to the kinking is reduced and lamellary atelectasis develops. These lamellary lesions might be termed 'secondary' or 'torsion' atelectases of the lingula, the torsion here referring to the anterior and downward rotation of the upper lobe.

The association of atelectasis of the lower lobe and torsion atelectasis of the lobe above it is a fairly common combination. It occurs characteristically on the left side, possibly owing to the fact that the course of the lingula bronchi to the diaphragm is steeper than that of the middle lobe bronchi. They are therefore more liable to kinking against the diaphragm on anterior and downward rotation than the middle lobe bronchi. The elevation of the right cupola of the diaphragm in lower lobe atelectasis of the right lung is less marked than that of the left cupola in left lower lobe atelectasis.

The atelectatic complex of the left lung described in the present paper is important from a diagnostic standpoint. An obvious lamellary 'secondary' atelectasis of the lingula may mask the presence of a more important massive atelectasis of the lower lobe so that it escapes detection. Secondary atelectasis or, as it may be termed, torsion atelectasis seems to be confined to the left lung.

SUMMARY

Lamellary atelectasis affecting the lingula, combined with atelectasis of the lower lobe is discussed and its pathogenesis explained.

ZUSAMMENFASSUNG

Lamelläre Atelektase der Lingula kombiniert mit Atelektase des Unterlappens werden besprochen und ihre Pathogenese erklärt.

RÉSUMÉ

Les auteurs étudient l'atélectasie lamellaire de la lingula associée à l'atélectasie du lobe inférieur et expliquent sa pathogénie.

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LOCALIZED EMPHYSEMA

by

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Solitary or multiple cavities of the lungs are generally called 'cysts'. A multitude of abnormalities of widely different aetiology have been reported under this designation and as a result the nomenclature covering abnormal air-filled cavities of the lungs has become rather confused.

One of these conditions of increased air content in the pulmonary tissue is localized emphysema which has received comparatively little attention. MILLER (1929) was among the first to describe localized emphysema. He made a distinction between various sub-groups, introducing the term 'bulla' which he took to mean a collection of dilated alveoli where atrophy and rupture of the alveolar walls had given rise to a single air-filled cavity of varying size. A ruptured (dilated) peripheral alveolus filled with air, between the pulmonary tissue and the visceral pleura, he called a 'bleb'. (If the visceral pleura ruptures as well the result is not a bleb but pneumothorax.)

Bullae are frequently multiple to make up a major or minor localized emphysematous area. The appearance of the surface structure of such an area suggests a bunch of grapes. In extreme cases an entire lobe may be involved, when the condition is called lobar emphysema. There is thus a gradation from isolated bullae to lobar, localized emphysema, and it

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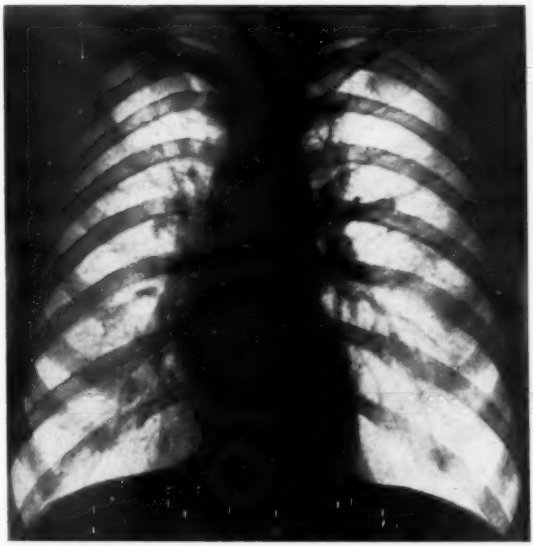

Fig. 1. Case 1. Inspiration. The localized emphysema on the left base is hardly discernible.

seems reasonable to consider all cases of blebs, bullae, and localized emphysema as one clinical entity.

The pathogenesis is now considered by most authors (CAFFEY, SHAW, HEAD and others) to be a check-valve mechanism in an afferent bronchial branch. A valve may be formed by mucosal hypertrophy, allowing the air to pass into the alveoli but not to escape again. WESTERMARK believes (1948) that it must be during a paroxysm of coughing, or the like, that the air is forced past the valve, ordinary breathing movements being too weak to overcome the obstruction, and that these factors form the condition for distending the alveoli and gradually leading to bullae.

Mucosal hypertrophy is not always present in cases of localized emphysema, the valve mechanism then appearing to be due to deficient development or possibly the total absence of cartilaginous rings in the bronchial branch concerned (SHAW 1952).

Localized emphysema may in rare cases co-exist with central, bronchogenic tumours (WESTERMARK 1948). In such instances, it is a sign of partial occlusion of a bronchus; total occlusion causes atelectasis. The localized emphysema thus represents an early stage of the obstructive lesion which may be followed by atelectasis at a later stage. ROBERTSON & JAMES (1951), in 5 cases of children with localized emphysema, found 2

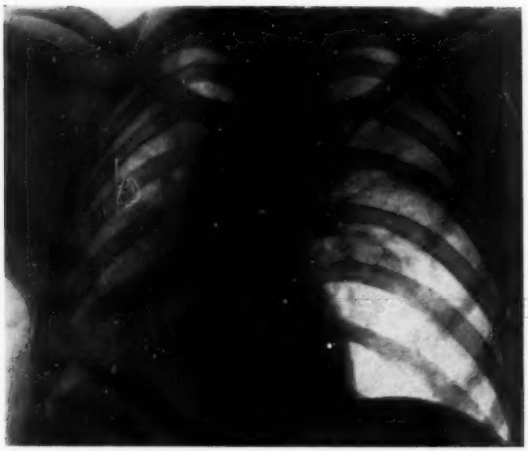

Fig. 2. Case 1 (same as in fig. 1). Expiration. The emphysema is now evident. Marked displacement of mediastinum.

with mucous valves and 1 with an aneurysmal vascular ring which had compressed the bronchus. (In the remaining 2 cases they could find no explanation for the condition.)

The clinical findings depend mainly on the size of the localized emphysema. Many cases are asymptomatic until secondary infection occurs in the involved area; incidentally, secondary infection is fairly uncommon in localized emphysema as compared with, for example, pulmonary cysts (NACLERIO & LANGER 1947). Localized emphysema is thus not uncommonly a chance finding in routine investigations.

The most important sign is dyspnoea, usually only on exertion. Cough, expectoration, and chest pain are not uncommon, whereas haemoptysis rarely occurs, and if so generally because of the causative obstruction (e. g. a bronchogenic tumour). In other words, the signs and symptoms are not typical, as they may accompany other diseases of the lung. At times, however, rupture of a peripheral alveolus may give rise to spontaneous pneumothorax, which is then almost pathognomonic of localized emphysema or isolated bullae (CURTI & THUE POULSEN 1950).

Localized emphysema is characterized roentgenologically by an area more translucent than the remainder of the lung. There is as a rule no distinct demarcation between the adjacent healthy parenchyma, although in a few cases it may be indicated by a thin line. This is in contrast to actual cysts of the lung which are nearly always surrounded by a fairly distinct wall. The emphysematous area compresses the adjacent pul-

nary tissue, leading to a more or less extensive atelectasis, although as a matter of fact the latter is seen most often when large areas of the lung are involved. Displacement of the mediastinum is common.

Isolated blebs are extremely difficult to diagnose in an intact lung. In pneumothorax is present, however, small annular structures may be discernible on the surface of the lung. These structures cannot, however, be distinguished with certainty from the far more common bullae; unlike the blebs, they are also demonstrable in the fully expanded lung. Multiple bullae generally form a honeycomb structure in the affected area; they may often be difficult to differentiate from bronchiectases or pulmonary cysts, and the final diagnosis must usually await operation and microscopic examination of the diseased tissue.

Fluoroscopy will show less effective emptying of the involved lobe in a case of localized emphysema although at times the emphysema is not seen until the expiratory phase (Figs. 1 and 2). If there is a suggestion of emphysema, it is advisable to obtain films in inspiration as well as expiration.

It will be evident on microscopic examination that the changes are confined to the alveoli whose walls are atrophic or ruptured. The walls of dilated cavities are lined with flattened endothelial cells. No pathologic changes are present in bronchioles or the larger bronchi; this is in contrast to the findings in cysts of the lung where the changes involve the bronchioles, and in bronchiectases where the dilatation affects larger as well as smaller bronchi, leaving the alveoli intact (CAFFEY 1940).

Present series

Fourteen cases of localized emphysema were studied with special regard to the pathogenesis. The patients, 6 males and 8 females, ranged in age from 12 to 62 years. Three had no symptoms, and localized emphysema was an incidental finding in routine investigations. The others had dyspnoea, chest pain, and/or cough; the respiratory symptoms had generally been of relatively short duration, and in only one had extended over several years. In the fourteen cases, the changes were located in the right upper lobe in 4, and in the right lower lobe in 2 cases; in no case were they observed in the right middle lobe. On the left side they were present in the upper lobe in 3 cases, in the lingula in 3, and in the lower lobe in 3 cases.

Five patients had small collections of bullae involving a relatively small proportion of a lobe, while in the others the localized emphysema involved a large segment or an entire lobe, leading to more or less extensive atelectasis of the surrounding parenchyma and usually to displacement of the mediastinum to the contralateral side.

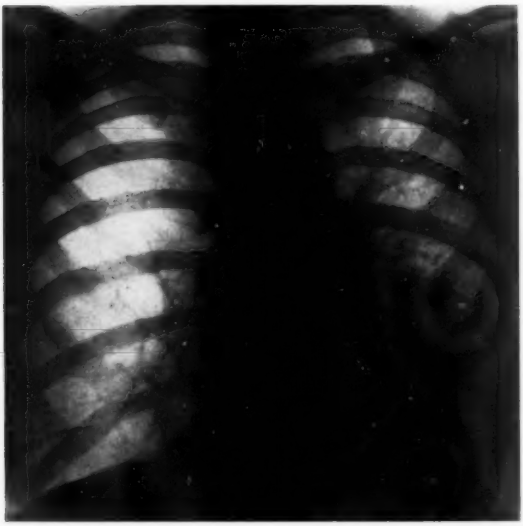

Fig. 3. Case 3. Marked emphysema of right basal lobe.

A reasonable explanation of the origin of the emphysema was found in only four cases, whereas in the others the mechanism remained unelucidated. The four cases reported below all raised the question of a valve mechanism being present.

Case 1 (Figs. 1 and 2). Male, aged 27. No pulmonary symptoms apart from vague sensations in the left chest. On routine chest roentgenography, the left lower zone showed considerably increased translucency, especially on expiration. On bronchography the contrast medium was held up in the lingular branches. The apical and basal lobe branches were pressed backwards and upwards by a large emphysematous lingula. Left-sided thoracotomy with lingulectomy was performed. A hilar lymph node, the size of a hazel nut, had presumably compressed the two lingular bronchi.

Case 2. Female, aged 15. History of pneumonia at the age of 6 years when a round density at the right hilum as well as emphysema of the right lower zone, displacing the heart to the left, were observed on roentgenography of the chest. After being followed up for several years without any improvement worth mentioning, the patient was referred for surgery. On right-sided thoracotomy, a cyst, the size of a tangerine, was found arising from and compressing the right lower lobe bronchus. The lower lobe was markedly emphysematous and occupied the greater part of the right chest. The apical and middle lobes were compressed but were otherwise normal. The cyst and the right lower lobe were removed.

Microscopic examination of the lobe showed large, irregular alveoli with atropic, partially defective walls; the cyst proved to be of bronchogenic origin. In this case, the localized emphysema had clearly arisen as a result of partial bronchial obstruction with a valve mechanism caused by the pulmonary cyst.

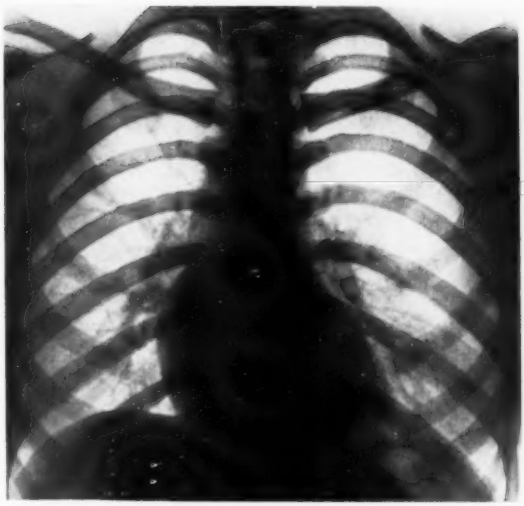

Fig. 4. Case 4. Definite emphysema of left apical lobe.

Case 3 (Fig. 3). Female, aged 35, with attacks of fever, chest pain, dyspnoea, and cough for 11 years. She had been admitted to hospital several times with 'pneumonia'. Roentgenography revealed typical localized emphysema of the right lower pulmonary lobe with displacement of the mediastinum to the left. Bronchography gave no further information except poor filling of scattered branches of the lower lobe. Right lower lobectomy was carried out. The right lower lobe bronchus was appreciably softer than normal and there seemed to have been a question of a valve mechanism caused by the pressure of the surrounding parenchyma upon the chondromalacic bronchus.

Case 4 (Fig. 4). Female, aged 13, asymptomatic. Routine investigation of the lungs revealed a typical translucent area in the left apical zone with displacement of the mediastinum to the left. Bronchography showed poor filling of the very small-calibred dorsal bronchial branch of the apical lobe, the emphysema involving the area supplied by this branch. Left exploratory thoracotomy disclosed that this segment was large and emphysematous. There were no signs of bullae, blebs, or cysts on the surface; the segment seemed to be functioning and was therefore not resected.

In this case we have no definite explanation of the localized emphysema, but it is reasonable to assume that it was related to the under-development of the associated bronchial branch. Repeat bronchography one year after the thoracotomy showed the emphysema to be unchanged; the dorsal branch in the left upper lobe segment remained small and narrowed.

SUMMARY

Localized emphysema with special reference to a material of 14 cases is discussed. Its clinical and roentgenologic features as well as various aetiologic factors are described. The concept of a valve mechanism is considered but it is pointed out that in many cases the pathogenesis remains obscure.

ZUSAMMENFASSUNG

Lokalisiertes Emphysem wird an Hand von 14 Fällen diskutiert. Das klinische und röntgenologische Bild, wie auch verschiedene äthiologische Faktoren werden beschrieben. Die Annahme eines Ventil-Mechanismus wird in Betracht gezogen, aber gleichzeitig darauf hingewiesen, dass in vielen Fällen die Pathogenese dunkel verbleibt.

RÉSUMÉ

Les auteurs étudient l'emphysème localisé, en se basant particulièrement sur une série de 14 cas. Ils en décrivent les signes cliniques et radiologiques, ainsi que divers facteurs étiologiques. Ils examinent le concept pathogénique du mécanisme de soupape mais insistent sur le fait que dans de nombreux cas la pathogénie demeure obscure.

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ROENTGEN INVESTIGATION OF THE CORONARY VEINS IN THE DOG

by

L. Di Guglielmo, V. Baldrighi, C. Montemartini and *A. Schifino*

The advent of thoracic aortography has made the study of the coronary arteries possible both in animals under experimental conditions and in living human subjects.

Several papers dealing with the appearances of the arteries have been published during the last few years but references to the coronary veins are still infrequent in the literature. AGUZZI et coll. have reported a case in which, during an angiocardiography, complete contrast filling of the coronary venous system was obtained as a secondary finding. A similar case was reported by OVENFORS, and two more cases by KJELLBERG et coll. Investigations on the coronary vein sinus by catheterization were performed by TORI.

In 1957 we reported our first observations on the roentgen appearances of the coronary veins in living dogs. The purpose of this paper is to report our further results in a greater number of cases under different experimental conditions.

Anatomy. A systemic description of the coronary veins in dogs appears in the papers published by CHAVEAU and by BEST and TAYLOR. From their findings and our own experiences, the anatomical features of these veins may be summarized as follows.

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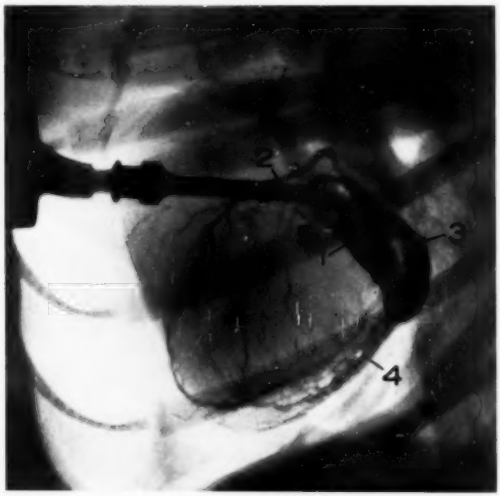


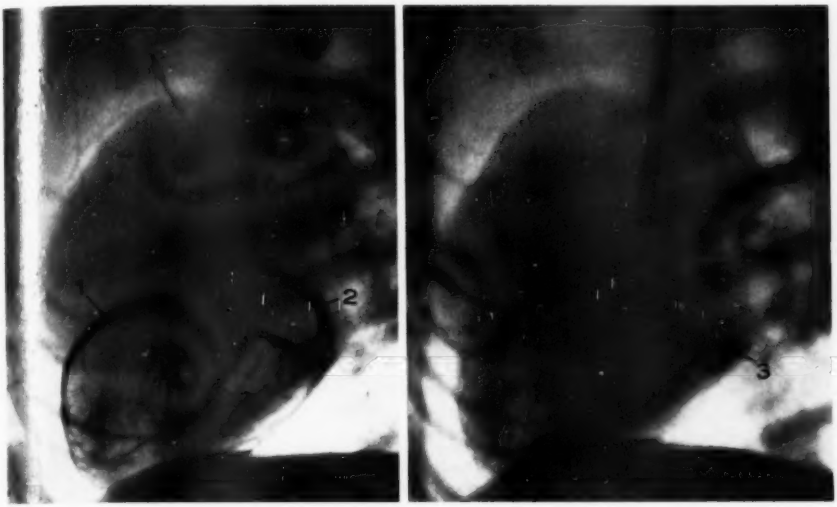
Fig. 1. Appearances of the coronary veins of a dog post mortem with the heart in situ. Contrast medium introduced into the coronary sinus. 1—venous coronary sinus, 2—ant. interventricular, 3—atrioventricular, and 4—post-interventricular parts of the vena cordis magna; 5—venae cordis anterieres.

The veins of the heart consist of a superficial and a deep system.

The superficial venous system (Fig. 1) is made up in the first place of a vein which arises in the anterior interventricular sulcus and turns to the left into the atrioventricular sulcus upon the dorsal surface of the heart. This vein is usually called the vena cordis magna. In the crux region on the dorsal surface of the heart it receives another vein from the posterior interventricular sulcus. The vena cordis magna runs into the venous coronary sinus, a large trunk, the length of which may vary to a considerable extent; it lies beneath the epicardium between the left auricle and left ventricle and runs to the posterior part of the right auricle in close proximity to the atrioventricular orifice. A few smaller veins, known as the venae cordis anteriores are present on the ventral aspect of the right ventricle and may vary in number from two to five.

The deep venous system consists of a number of small venules which originate from the myocardium and run directly into the cavities of the right heart, particularly the right auricle. These are known as the venae cordis minimae or thebesian veins.

The superficial venous system collects all the blood which originates from the left atrial and ventricular wall, as well as some of the blood



a b

Fig. 2. Angiography of the coronary system in a living dog. a) Arteriographic phase. 1 — ant. interventricular branch of left coronary artery, 2 — circumflex branch, 3 — post. interventricular branch, 4 — right coronary artery. b) Phlebographic phase. 1 — ant. interventricular vein, 2 — post. interventricular vein, 3 — semiannular atrio-ventricular part of the vena cordis magna. Increased density of right ventricle and right atrium, probably due to contrast medium passing directly into the heart chambers through the thebesian veins.

from the right ventricular wall. The deep system discharges through the thebesian veins all the blood from the right auricle wall (UNGER) as well as some of the blood from the right ventricle, directly into the heart chambers and particularly the auricle.

Material and Method

Our material consisted of 73 living dogs, all of medium or large size, in which 223 thoracic aortographies were carried out under different experimental conditions. The method used was described in our previous papers, to which reference should be made. Joduron 70 %, Pielosil 70 %, and Urografin 62 % were the contrast media of choice.

The intra-aortic blood pressure was followed in most tests by means of a Samborn electric manometer, and electrocardiograms were obtained from 36 subjects, while in 4 dogs, in addition to the arterial blood pressure, the coronary vein flow rate was checked during the injections of the contrast medium.

Results

When correctly performed, thoracic aortography invariably provides satisfactory filling of the coronary arteries. In 37 examinations, after the arteriographic coronary stage (Fig. 2a), appearances were obtained which may be positively attributed to venous circulation elements (Fig. 2b); these were clearly defined and reasonably constant in the various cases noted.

The contrast filling of the veins seems somehow to bear some relationship to the degree of filling of the coronary arteries, as evidenced by the fact that the phlebographic stage was constantly reached when a high concentration of contrast medium had been obtained in the coronary arteries. The opposite was not the case, however, i. e., good demonstration of the coronary arteries was not always accompanied by the appearance of the venous elements.

Our findings may be summarized as follows.

Interventricular veins (Fig. 2b). These are very seldom observed. The one usually seen is the anterior interventricular vein, although it is often not well defined. The posterior interventricular vein, close against the diaphragm, is still harder to identify. Other venous formations may sometimes be observed running alongside and nearly parallel to the interventricular branches to reach the atrioventricular sulcus.

The atrioventricular part of the vena cordis magna (Figs. 2b and 3). All the veins described so far reach the atrioventricular sulcus, whence they continue into a rather extensive, sharply outlined semiannular vascular formation situated between the left auricle and ventricle. Its width is fairly uniform, and only in a few rare instances can a localized increase in width be noted at its right extremity, i. e. at the level of the venous coronary sinus. In other words, no appreciable division can be defined in the living dog between the vena cordis magna and venous coronary sinus, which together form the vascular formation.

Contrast medium in the right chambers of the heart and of the pulmonary artery (Fig. 3). Contrast medium may be observed in the right auricle, right ventricle, pulmonary conus and sometimes in the pulmonary artery itself, simultaneously with, and often independently from, the findings described so far. While to some extent this is due to the contrast medium reaching the right auricle through the venous coronary sinus, it is mostly determined by the passage of the contrast medium from the right ventricular and auricular myocardium directly into the heart chambers through the venae cordis minimae.

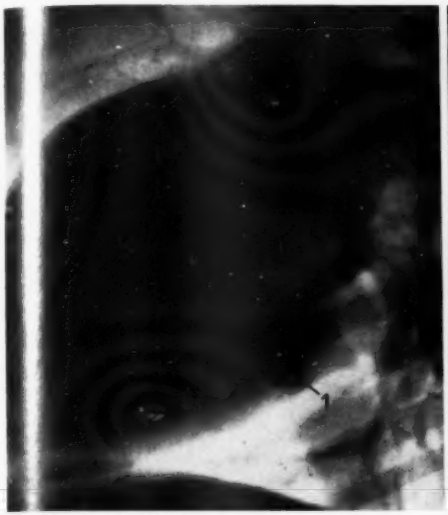


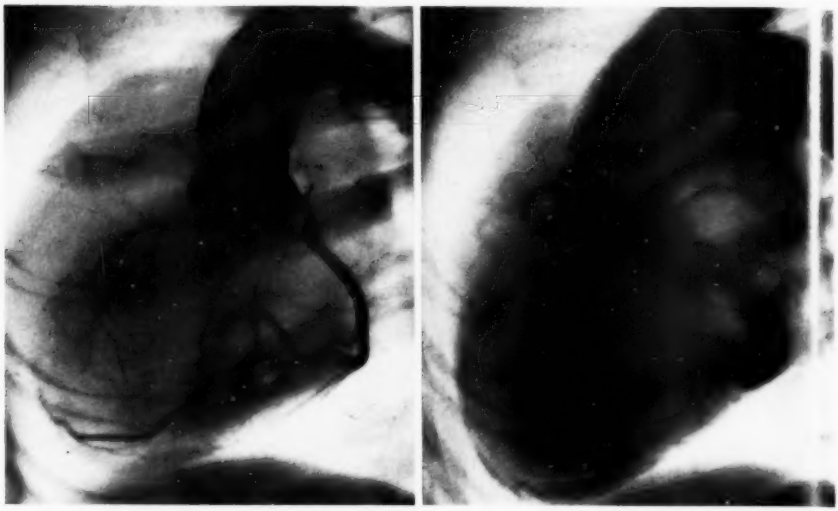
Fig. 3. Coronary angiography. Phlebographic phase. 1 – semiannular atrio-ventricular part of vena cordis magna. Marked increase in density of the right heart chambers and of the pulmonary arteries caused by the contrast medium passing through the thebesian veins.

Fig. 4. Simultaneous filling of coronary arteries and coronary veins after 0.2 mg of epinephrine. Semiannular atrio-ventricular part of vena cordis magna seen near circumflex branch of left coronary artery.

Effects of epinephrine and the epinephrine type of drugs upon coronary circulation. The action of epinephrine and certain epinephrine-type substances (such as Nor-epinephrine, Sympatol or Effortil) on the coronary vessels was investigated in 54 experiments. The effects on the coronary arteries have already been described and reference should therefore be made to our previous papers.

The following method was used. Thoracic aortography was performed under routine conditions and epinephrine (or other drug) then administered intravenously. As the hypertensive effect of epinephrine was observed a further contrast injection was made. Finally, approximately 20 minutes later, i. e. when the arterial blood pressure had reverted to its initial value, the last injection was given.

Contrast filling of the coronary veins is far more frequent and more dense after that any of the above drugs has been administered than under routine conditions and the filling occurs at an earlier stage, i. e. the time between the arterial and venous stages is considerably shorter than the normal 2 to 3 seconds. Frequently the veins appeared filled



a b

c

Fig. 5.

a) First examination. Roentgenologic appearances of coronary arteries under routine conditions.

b) Second examination, 20 min later, after injection of 0.2 mg Nor-epinephrine. Marked hypertension; simultaneous filling of aorta, coronary arteries, coronary veins, right heart chambers, and pulmonary arteries.

c) Third examination, 30 min later. Coronary arteries have now the same appearances as under routine conditions (a).

while the coronary arteries were still visible (Fig. 4). When the arterial blood pressure had reverted to its normal value 20 minutes after the administration of the drug, practically the same findings were recorded, for both the coronary veins and arteries, as had been obtained on the first examination. Identical effects were not produced by the four sub-

Fig. 6. Coronary angiography one month after surgical ligation of coronary sinus. Phlebographic phase. Persistent filling of a very enlarged anterior interventricular vein, coronary arteries normal.

stances used, a less intense action being observed with Nor-epinephrine, epinephrine, Sympatol and Effortil, in that order.

A most interesting finding was obtained from one of the dogs we examined after a Nor-epinephrine injection. Following the initial demonstration of the coronary system (Fig. 5a), 0.2 mg of the drug was injected intravenously. An exceptionally marked increase in arterial blood pressure was noted and, after the injection of a second dose of contrast medium, brief filling of the coronary arteries was followed by filling of the coronary veins, venous sinus, right chambers of the heart and pulmonary arteries (Fig. 5b). Such a finding would be hard to explain if there were no arterio-venous shunts allowing the contrast medium to flow from the arterioles to the venules directly. The intense contrast filling of the right chambers of the heart was evidence that a large amount of contrast medium had passed through the venae cordis minimae directly into the heart chambers. Twenty minutes later the arterial pressure had returned to normal, and following a further injection the findings closely resembled the initial ones (Fig. 5c).

Effects of epinephrine and the epinephrine type of drugs after the tying of a large coronary artery branch. Infarction was produced in 9 dogs by surgical ligation of a large coronary branch (the anterior interventricular

branch in 8 instances, and the posterior interventricular one in 1 instance). The condition of the coronary system was submitted to angiographic investigations 1, 2, 3, 4, 5, 12, 20, 30 and 62 days following the intervention, the examinations being repeated several times during two months on some of the subjects. As far as the coronary arteries and veins with infarction were concerned, the action developed by both epinephrine and the epinephrine type of drugs was found to be entirely similar to the one observed in these vessels under normal conditions.

Surgical ligation of the venous coronary sinus. The venous coronary sinus was ligatured in 3 dogs, and roentgen examination of the coronary system showed normal conditions of the coronary arteries, both as regards morphologic features and filling time. There was however considerable widening of the coronary veins, particularly of the anterior interventricular, in which the contrast medium stagnated for a long time (Fig. 6); contrast filling of the right chambers of the heart was also very marked.

Conclusion

When performed by the correct procedure, thoracic aortography in dogs makes it possible to demonstrate not only the coronary arteries but also, in a large number of cases, the venous coronary system. Contrast filling of the coronary veins is sometimes so dense as to allow an accurate roentgen investigation of the anatomical features of these veins.

Filling of the coronary veins after the arteriographic stage is not however constantly obtained. In a considerable number of cases, although complete filling of the coronary arteries was evident, no contrast medium could be observed in the veins. The most likely reason for this appears to be that since the heart is equipped with a capillary system which is so much more extensive than that of any other muscle, the contrast medium is considerably diluted; in addition to this, it will be so dispersed throughout both the superficial and deep veins that by the time it reaches the larger venous branches, its concentration will no longer be sufficient to render it roentgenographically demonstrable. Nor should the fact be disregarded that a large portion of the contrast medium is directly discharged into the heart chambers through the venae cordis minimae.

Very similar conditions perhaps exist in man, and are probably responsible for the fact that no coronary veins show up under roentgen examination in human subjects after the arteriographic stage even when the arteries have been completely filled.

The administration of epinephrine or epinephrine-type of drugs in dogs makes venous filling more frequent than under normal conditions. This may be explained by considering that these drugs exert a dilatory

ef ect on the coronary arteries, thereby enabling a larger share of contrast m dium to reach the coronary veins in a higher concentration and render tl m visible during the roentgen examination.

When an epinephrine-type of drug is administered, contrast filling oc urs within a shorter time than under normal conditions. This may po sibly be attributed not only to the dilatation of the coronary arteries, pe mitting a faster passage of the contrast medium into the veins, but in extreme cases also to the opening of arterio-venous shunts, enabling tl contrast medium to flow directly from the arterioles into the venules.

SUMMARY

The normal anatomy of the coronary veins in dogs is first described and followed by a report of an investigation of the veins based upon 223 thoracic aortographies in 73 living dogs. The changes of the coronary venous circulation under particular, experimentally induced conditions, are discussed with special reference to the effects produced by epinephrine, experimental infarction, and ligation of the coronary venous sinus.

ZUSAMMENFASSUNG

Es wird zuerst die normale Anatomie der Coronarvenen bei Hunden beschrieben und anschliessend über eine Untersuchung dieser Venen an Hand von 223 thorakalen Aortographien an 73 lebenden Hunden berichtet. Die Veränderungen der Coronarvenenzirkulation werden unter besonderen, experimentell beeinflussten Bedingungen, mit spezieller Hinsicht auf den Effekt von Epinephrin, experimentellem Infarkt und Ligatur des Sinus coronarius, besprochen.

RÉSUMÉ

Les auteurs décrivent d'abord l'anatomie normale des veines coronaires du chien, puis présentent une étude de ces veines, basée sur 223 aortographies thoraciques faites sur 73 chiens vivants. Ils étudient les modifications de la circulation coronaire veineuse dans des conditions particulières, crées expérimentalement, et spécialement les effets de l'épinéphrine, de l'infarctus expérimental et de la ligature du sinus coronaire veineux.

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PNEUMOPELVIGRAPHY OF DEVELOPMENTAL MALFORMATIONS OF THE FEMALE INTERNAL GENITALIA

by

M. Henzl, J. Horský, J. Presl and *M. Valenta*

Insufflation of gas into the peritoneal cavity for the roentgenologic demonstration of pelvic viscera in women has been used chiefly for estimating ovarian enlargement in the Stein-Leventhal syndrome and for the detection of tumours. Relatively little attention has been devoted to widening the application of this method to the diagnosis of the defective development of the female internal genital organs. We have found only one article dealing with this topic and few references to it in the literature.

Roux et coll. (1954) reported two cases, one of congenital absence of the ovaries and the second of congenital absence of the uterus, in which the diagnosis was established by pneumopelvigraphy (PPG). Winter and Perlmutter (1955) mentioned one case of genital malformation, without giving details. Houlné (1957) published one case of ovarian aplasia and one case of absence of the uterus with one normal ovary. Bompiani and Rigat (1958) reported six cases of various malformations of the internal genitalia. The most extensive report is that of Kunstadter (1954), who presented his experience with PPG in children with various endocrinologic diseases. It is the aim of this study to discuss the potentialities of the PPG as a means of differentiating developmental disturbances.

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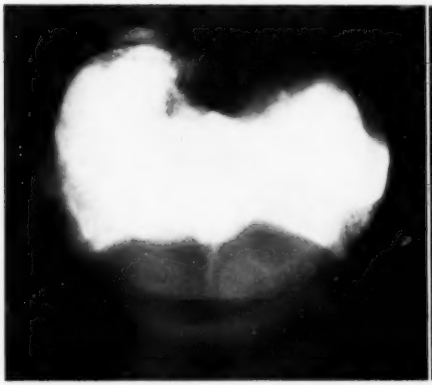


Fig. 1. Both ovaries absent.

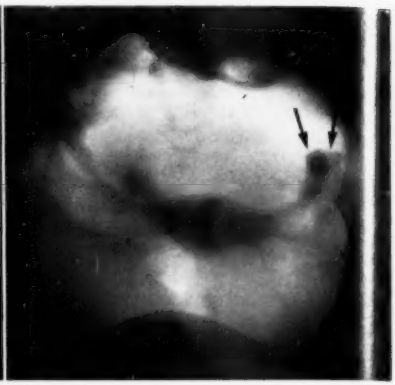


Fig. 2. Flat ovarian rudiment (↔), ampulla of Fallopian tube viewed end on (→).

Method. The skin, subcutaneous tissue and fascia are infiltrated with 0.5 % novocaine, two fingers below and lateral to the umbilicus, and a spinal needle introduced. As the point of the needle passes through the abdominal wall, two resistances are felt, those of the deep fascia and the peritoneum. If local anesthesia is complete, no pain is felt when the point pierces the peritoneum. To make sure that the needle lies correctly we first inject 2 to 4 ml of air and listen for the typical sound of escaping gas, as is heard during kymoinsufflation. The piston of the syringe must slide quite freely with virtually no pressure of the fingers. Carbon dioxide, 1 300 to 1 600 ml. is then allowed to flow in at a pressure of 20 to 40 mm Hg. After the filling, the patient assumes the knee-chest position, and the intestines are displaced toward the diaphragm by pressure on the abdominal wall. Three antero-posterior films are usually taken.

Fig. 3. Small right ovary (→), rudiment on left side (↔). Fallopian tube (↔).

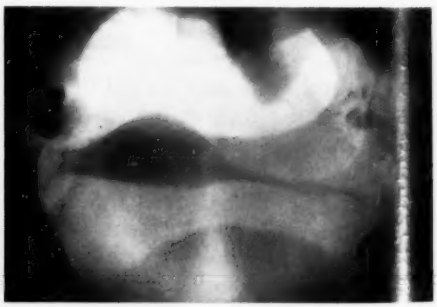


Fig. 4. Hypoplastic uterus, calcifications in the adnexa.

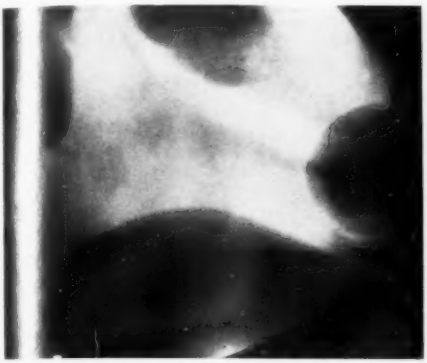


Fig. 5. Congenital absence of uterus.

Fig. 6. Congenital absence of uterus, remnants of lateral portions of Müllerian ducts.

Results

Over the past 3 years we have performed 170 pneumopelvigraphic investigations, 23 of them in suspected developmental abnormalities. In two cases the examination failed because of extreme obesity. The remaining 21 cases could be divided into the following groups:

A. *Developmental defects of the ovaries*

1. Ovaries absent (5 cases)
2. Rudimentary or extremely hypoplastic ovaries (2 cases)
3. Unilateral development of the ovary (1 case)
4. Developmental disturbances secondary to infection, etc (2 cases)

B. *Developmental defects of the uterus*

1. Congenital absence of the uterus (4 cases)
2. Uterine deformities, such as bicornuate, unicornuate, septate uterus, etc (7 cases).

Case reports

One typical case in each group is presented below.

Case 1. Ovaries absent. N. B. Aged 17 years, primary amenorrhoea with retarded growth, signs of Turner's syndrome, and absence of the vagina; chromatine pattern masculine. PPG (Fig. 1) revealed a narrow band extending between the ischial spines, with a small ovoid density in the midline. The former corresponds to a peritoneal duplication containing a rudimentary uterus and Fallopian tubes. There is no evidence of ovaries on either side. Final diagnosis: Gonadal aplasia.

Fig. 7. Bicornuate uterus. Two separate soft tissue masses.

Case 2. Rudimentary or extremely hypoplastic ovaries. S. A. Aged 17 years, primary amenorrhoea with retarded growth. PPG (Fig. 2) revealed an infantile uterus with ligaments, to the lateral ends of which small flat ovarian rudiments were attached. On the rigth side a round density, the ampulla of the Fallopian tube is seen. Final diagnosis: Extreme ovarian hypoplasia.

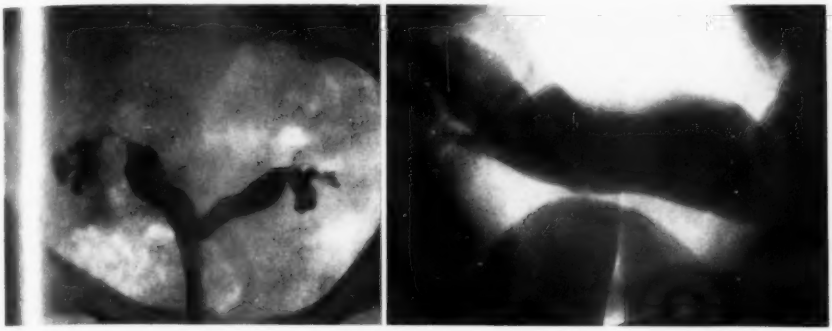
Comments: According to the clinical and laboratory findings, all patients in the first two groups may be classified with the variants of the syndrome of gonadal dysgenesis (WILKINS), with elevated urinary gonadotrophins (more than 64 M. U.) and with clinical signs of Turner's syndrome, more or less marked. The next group may be regarded as a border-line one, the ovary being relatively well developed, although only on one side.

Case 3. Unilateral development of the ovary. P. M. aged 30 years, primary amenorrhoea. PPG (Fig. 3) shows a hypoplastic uterus, somewhat deviated to the right. From the right cornus the Fallopian tube runs to the pelvic brim, where it is overlapped by an ovary of nearly normal size. The left ovary cannot be identified; the widening of the ligament appears to be an ovarian rudiment.

Case 4. Developmental disturbances secondary to infection, etc. K. M. aged 23 years, from childhood treated for pulmonary tuberculosis. PPG (Fig. 4) revealed a hypoplastic, infantile uterus, deviated to the right, on which side a small ovary with dense calcifications can be seen. Similar formations are visible, on the left side.

Comment: The patients in group A-4 differ from the previous ones in that embryonal development was basically normal but the genital tract was damaged by a tuberculous process probably during postnatal life.

Case 5. Congenital absence of the uterus. K. A. aged 23 years, primary amenorrhoea. aplasia of the vagina. PPG (Fig. 5) disclosed well-formed ovaries and two broad bands, 3 to 4 cm in length, running from the inner edge of the ovaries towards the middle. There was no trace of any uterus.



a b

Fig. 5. a) Hysterogram of a bicornuate uterus, which in the pneumopelvigram (b) is seen as a bent cylinder.

Case 6. Group B-1, as in Case 5. S. M. aged 21 years, primary amenorrhoea, aplasia of the vagina. PPG (Fig. 6) revealed normal ovaries, between which ran a narrow band with a funnel-shaped widening at both ends. At laparotomy the bands near the ovaries were revealed to be duplications of the pelvic peritoneum, containing funnel-shaped structures emptying into Fallopian tubes. They may be regarded as remnants of the lateral portion of Müllerian ducts.

As to the group B-2 (uterine deformities, such as bicornuate, unicornuate, septate uterus, etc) we wished to determine if the PPG would contribute to the differential diagnosis of bicornuate and septate uterus. The hysterograms of both deformities are often very similar (Figs. 8a, 9a). At PPG the bicornuate uterus is seen as two soft tissue masses joined in the midline (Fig. 7); in the case demonstrated, there is a band running from the area of the cervix to the sacral region. When the two cornua are closer to each other, the uterus appears as a bent cylinder (Fig. 8b), in contrast to the septate uterus which projects as an oval silhouette (Fig. 9b). Its width depends on the angle subtained by both parts of the uterine cavity. The outline is convex antero-posteriorly.

Discussion

In analysing these 21 cases, it was possible to demonstrate the roentgen appearences of various anomalies of the female internal genital tract, from the more marked to the relatively less important ones. PPG supplemented the clinical and laboratory diagnoses, chiefly in cases of gonadal dysgenesis (WILKINS), being of value, for instance, in the differential diagnosis between pituitary dwarfism and retardation of growth due to gonadal hypofunction. In our series, there were no hyperplastic ovaries combined with primary amenorrhoea, which condition may also be regarded as a congenital anomaly (STANGE 1956). In such a case, PPG would provide a rapid and significant diagnosis without laparotomy, which would otherwise be necessary.

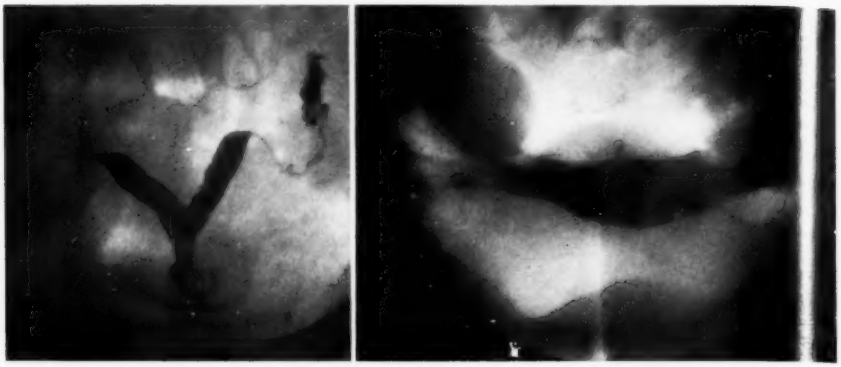


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Fig. 9. a) Hysterogram of a septate uterus, which in the pneumopelvigram (b) is projected as an oval silhouette.

The relative value of PPG in comparison with culdoscopy, laparoscopy and exploratory laparotomy is that the three latter procedures must be regarded as surgical interventions, carrying certain risks. PPG, on the other hand, is a simple and safe method for the demonstration of the pelvic organs. One of the advantages of PPG lies in the possibility of making a differential diagnosis between bicornuate and septate uterus. Bimanual palpation is not always reliable and the hysterograms often show similar appearances. Even in modern textbooks of gynecologic roentgenology (FINKBEINER, SCHULTZE, SNOW) it is stated that the degree of malformation may be demonstrated only at the time of operation. PPG, on the contrary, gives us a more accurate picture of the extent of pathology, and in this way enables us to draw the necessary conclusions as to the prognosis and indications for corrective surgery.

Laparotomy seems to be indicated in cases of suspected testicular feminisation (MORRIS) where the remnants of testicular tissue may give rise to tumours with a nearly 10 % malignancy rate, and for which reason removal of the abnormal gonads is indicated. Since the question of possibly malignant degeneration in ovarian remnants is not settled as yet, we are not justified in insisting upon operation, which in any event is often refused by the patient.

PPG thus remains the only method by which we may obtain with very little risk sufficient information to clarify the nature of anomalies in the pelvis.

Conclusions

PG represents a valuable method for diagnosing anomalies of the fe e genital tract, particularly in disturbances of the general development (sy rome of gonadal dysgenesis, adrenogenital syndrome, pituitary dwarf- isn etc), disturbances in the development of the urogenital sinus (atresia an tenosis of the vagina), in cases of primary amenorrhoea, menstrual dis ders of the hypohormonal type in virgins, and uterine deformities.

SUMMARY

Twenty-one women with various anomalies of the genital organs were investigated by eans of pneumoperitoneum. Descriptions of 6 typical cases are given. Pneumopelvigra y is considered a simple method and relatively safe in comparison to other explorative pro dures.

ZUSAMMENFASSUNG

Einundzwanzig Frauen mit verschiedenen Anomalien der Genitalorgane wurden mittels Pneumoperitoneum untersucht. Es werden sechs typische Fälle beschrieben. Pneumopelvigraphie wird als eine einfache Untersuchungsmethode angesehen und ist, im Vergleich mit anderen Methoden, relativ gefahrlos.

RÉSUMÉ

Les auteurs ont examiné par pneumopéritoine vingt et une femmes présentant diverses anomalies des organes génitaux. Ils décrivent 6 cas typiques. Ils considèrent que la pneumopelvigraphie est une méthode simple, et, par comparaison avec d'autres techniques d'exploration, relativement sans danger.

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MIMER

by

G. Fredzell and *E. Lindgren*

The progressive development of apparatus and equipment for use in roentgen examinations has in general followed two main lines, one representing equipment for fluoroscopy from different angles with added facilities for the exposure of films, with or without spot film devices, and the other covering apparatus for examinations which do not as a rule require fluoroscopy, i. e. most skeletal examinations. The variations in design and construction are greater among the units ranged in the first mentioned group than in the latter, although the present industrial trend to manufacture in series may contribute towards equalizing the individual demands of roentgenologists. If tomography equipment is excepted, units for skeletal examinations show more uniformity and simplicity of design but do not as a rule permit of precision in projection. It is in fact surprising to find from textbooks for radiographers, and similar literature, how often authors appear to ignore the means of obtaining a satisfactory demonstration of anatomic detail. The highest degree of accuracy in the directioning of the central ray in relation to the object to be examined is necessary for a clear rendering of a given anatomic detail and for ensuring the possibility of reproducing exactly the same projection at a later occasion. This is essential for a comparison of roentgen views from different examinations and for an evaluation of any changes in a pathologic condition.

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The requirements just mentioned are without doubt of particular importance in connection with roentgen examinations of the skull. It is a fact that the only unit which can be regarded as meeting these demands is the so-called 'skull table' designed by LYSHOLM (manufactured by Schönanders), the prototype of which was described in 1925. It was originally intended for the roentgen examination of the nasal sinuses and auditory cell system but was modified in 1931 and then adapted for examinations of the entire skull. The application of the basic theoretical principles resulted in a construction which in practice left much to be desired; in fact, the unit did not correspond to the original intentions. This was on the other hand the case with the new model which was put on the market in 1935 and which today, after 25 years, retains the same general appearance. This is a long period for a roentgenographic unit and indicates that the fundamental principles of the design were sound and that the construction had been so carefully worked out that no significant improvements had been considered necessary. Another indication of the suitability of the unit is the fact that the original design has been copied, more or less openly.

As the name indicates, the skull table was originally intended for examinations of the bones of the skull, but is used with advantage for the examination also of other skeletal parts, as well as for arthrography. When ventriculography became a routine procedure the skull table was found particularly valuable also for such examinations. The rapid development of ventriculography under the direction of LYSHOLM was essentially made possible by the facilities afforded by this unit of producing accurately the various projections in different planes which were required. In modern neuroradiologic procedures, however, encephalography and angiography prevail, and in these examinations there are undoubtedly certain inherent disadvantages connected with the use of the present skull table.

We have for a long time felt the need for a new unit which, without neglecting the basically sound principles of the original design, would better correspond to requirements arising in modern neuroradiologic work. As, however, the relative amount of neuroradiologic work in many hospitals is not very large, it seemed expedient to attempt to achieve a design which would be well suited for carrying out other types of roentgen examinations as well. Another factor to be kept in mind was that no satisfactory device for the delicate handling of severely injured patients during roentgen examination appeared to exist. The filling of this gap was therefore our further aim. Various technical solutions have been put to trial, and many small as well as full size models have been tried out in practice before a construction satisfying our demands was achieved.

The new diagnostic roentgen unit, which we call Mimer, is fitted with a roentgen tube which can be freely rotated and directed onto any point on a spherical surface with a radius of 80 to 90 cm (Fig. 2). The centre

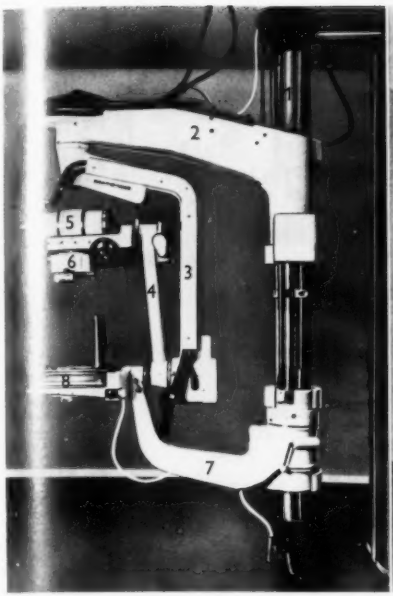

Fig. 1.

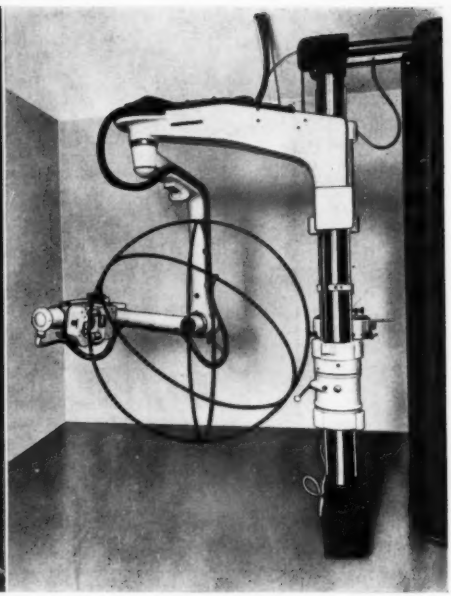

Fig. 2.

Fig. 1. The Mimer installation. 1 — Wall-floor stand, 2 — Cantilever, 3 — Vertical arm, 4 — Tube arm, 5 — Roentgen tube, 6 — Primary diaphragm, 7 — Support arm for object table, 8 — Object table.

Fig. 2. The ranges of rotation of the roentgen tube are indicated by the three circles.

of this sphere can be moved for a distance of 60 cm in a vertical direction. In the Lysholm skull table the focus-film distance is comparatively short, whereas in the imitations this distance has been considerably increased, often on the pretext that in comparison with the original skull table this constituted an advantage. Some lack of appreciation of the importance of drawing full benefit from the divergence of the beam of rays is revealed in this reasoning, however. The various anatomic parts of the skull, since they are at different distances from the film, will at a short focus-film distance appear with different degrees of sharpness; and these distance differences in the skull are of such a magnitude that views produced under such conditions assume a three-dimensional aspect which often makes stereoscopy superfluous. The radiation intensity losses are moreover smaller, which facilitates the use of a fine-focus tube. We have therefore considered it appropriate to retain a relatively short focus-film distance for the new unit.

It also seemed necessary that, in contradistinction to the earlier skull table, the new roentgendiagnostic unit should enable fluoroscopy in differ-

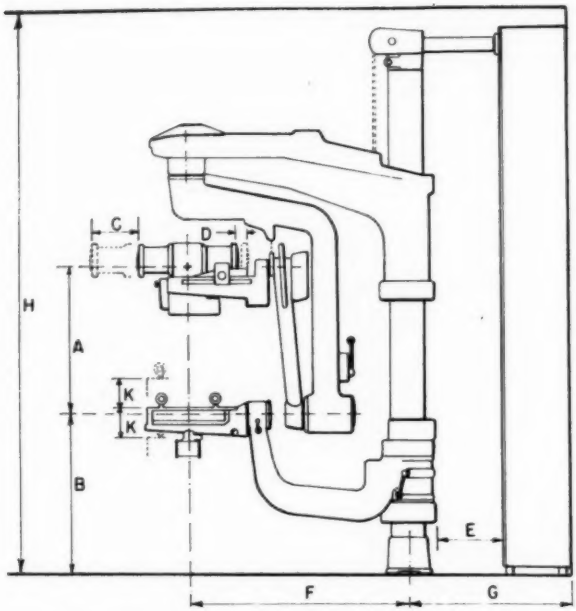

Fig. 3. Schematic drawing of Mimer as seen from the side.

The letters correspond to the following measures in millimeters:
A = 800, B = 1 360—760, C = 250, D = 60, E = 370, F = 1 230, G = 900, H ≥ 3 000, K = 100.

ent directions to be performed. Many skeletal examinations are no doubt facilitated if accurate positioning can be achieved with the aid of fluoroscopy, and for the examination of severely injured patients we regard it imperative that this possibility be provided.

Technical description of Mimer

A cantilever is mounted at the upper part of a wall-floor stand, a practically downward-directed, vertically movable arm being suspended at the free end of the cantilever (Fig. 1). An upward-directed pivot arm, which carries the roentgen tube and which we call the tube arm, is mounted at the lower end of the movable arm and articulates with it. These two arms form a V when the roentgen tube is in the zero position. The tube rotates on a horizontal axis, and the vertical arm (suspended from the cantilever) on a vertical axis. The articulating connection between the two arms is at the same level as the plane of the film.

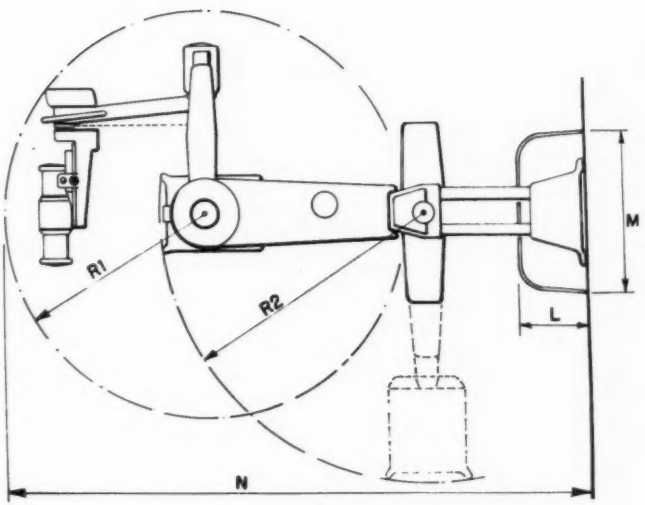

Fig. 4. Schematic drawing of Mimer as seen from above.
The letters correspond to the following measures in millimeters:
L = 370, M = 870, N = 3 240, R1 = 1 110, R2 = 1 480.

Another arm, mounted at the lower part of the wall-floor stand, supports the object table which latter is provided with a secondary grid. This arm can be swung aside to obtain free floor space beneath the roentgen tube, where a film changer unit, a stretcher, or a mobile examination couch may be placed in position, as necessary. A fluoroscopic screen with cassette holder can be attached to the tube arm, and the whole tube-screen assembly turned around the patient so that fluoroscopy and roentgenography can be carried out from any desired direction. A combination of movements of the vertical arm and the tube arm enables the focal spot to be placed anywhere on the spherical surface. The central ray is normally directed towards the centre of a sphere of a radius of 80 cm. Any focus-film distance between 70 and 90 cm may, however, be employed by raising or lowering the object table. The central ray may also be decentralized either by a lateral shift of the roentgen tube or by tilting the carriage on which the tube is mounted. The direction of the central ray is indicated by a light pointer. The centre of the sphere is normally at the same level as the centre of the object table, with a possible maximal movement of 60 cm in a vertical direction. The movement of the tube is operated electrically by means of a multi-velocity control which allows rapid changes of direction and a fine adjustment at the selected level. The position of the roentgen tube is altered by built-in

and remote-controlled motors by which means the movements are rendered effortless.

A clear perspex sheet is fitted in the centre of the top of the object table and the same mirror device as in the earlier skull table is used for observation of the object from below during the positioning, a principle of construction which has proved to be fundamentally sound. A secondary grid and a separate tray for cassettes up to a film size of 30 cm square are accommodated beneath the perspex sheet. The tray can be removed together with or without the grid and both can be rotated for oblique projections. Scales indicate the rotation of the grid in relation to the tube.

The outer dimensions of Mimer are given in the legends to the schematic drawings in Figs 3 and 4. The height of the ceiling of the room in which the unit is installed should not be less than 3 metres because if lower the vertical movement is correspondingly reduced. The unit is provided with several counter-weights, and parts of this counter-balancing system are housed in a wall-mounted cabinet which extends about 32 cm from the wall. We have found it convenient to install the control panel at the side of this wall cabinet. This panel, which measures 80 × 58 × 25 cm, contains the regulating devices for changing the focus-film distance, for the lock and emergency brake of the tube arm, and for the tomographic equipment. The latter is at present substituted for the object table during tomography, which can be performed within an arc of 300°. The distances between the parts of the equipment mounted on the wall and the wall-floor stand can of course be varied to allow for local conditions but it is advisable to provide for the free passage of one operator. As Mimer covers a floor space of about 3.25 × 3 metres, the dimensions of the room in which it is to be installed should not be much less than 4 × 5 metres.

SUMMARY

A new roentgendiagnostic unit, called Mimer, is described. It is particularly suitable for neuroradiologic investigations but is also useful for other types of roentgen examinations.

ZUSAMMENFASSUNG

Ein neues röntgendiagnostisches Gerät, genannt »Mimer«, wird beschrieben. Es ist besonders für neuroradiologische Untersuchungen geeignet, aber auch für andere Gebiete der Röntgendiagnostik verwendbar.

RÉSUMÉ

Les auteurs décrivent un nouvel appareil de radiodiagnostic appelé Mimer. Il est particulièrement adapté aux examens neuroradiologiques, mais est aussi utile pour d'autres types d'examens radiologiques.

FE 4 THE RESEARCH LABORATORIES, EASTMAN KODAK COMPANY, ROCHESTER 4, N. Y., U. S. A.

NEW STEPPED WEDGES FOR RADIOGRAPHY

by

H. E. Seemann and *B. Roth*

It is our purpose in this paper to describe two new designs of stepped wedge, one made of aluminum for use in film studies, the other made of a plastic for use in establishing uniform radiographic techniques for the heavier body parts. Both designs are directed toward the attainment of results which are more quantitative in their respective fields of application than has been usual in the past. The designs are the result of empirical trials and therefore may not be the only forms which would be satisfactory. They are simple enough to be built by a mechanic who has reasonable skill.

Limitations of conventional wedges. There are serious pitfalls if one attempts to obtain quantitative results with the usual type of wedge because the percent change in intensity from step to step is much greater at the thin end than at the thick end of the wedge. However, to have a stepped wedge, simple to use, it is essential that the percent change per step along the entire wedge should be constant. The reason for this requirement will be discussed later. (A wedge having this feature was described several years ago (Corney & Seemann 1947) but its construction involved more empirical testing than seems warranted, now that an improved design has been worked out.)

Presented, under a slightly different title, at the 9th Intern. Congr. of Radiology in Munich, July 1959. Submitted for publication 26 October 1959.

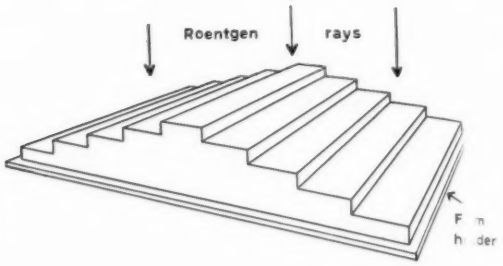

Fig. 1. Schematic drawing of an improved design of stepped wedge. It contains a filter and mask within the base.

In addition to the unequal percent changes per step, the conventional wedge has another drawback as far as practical use is concerned. With inadequate agitation, greater uniformity of development of a strip of film is usually obtained if the high-density end is down in the tank of developer. The operator must provide for this and must strive for good agitation. A false contrast will be obtained if development is not uniform along the length of the film strip.

The distribution of scattered radiation is not uniform under a wedge near its periphery, the effect being dependent on the amount of scatter from various thicknesses of the wedge and the amount of 'undercut' from the immediate surroundings. To reduce the disturbance from this effect the dimensions of the wedge must be generous so that densities can always be read centrally where uniformity prevails and where the exact location of the density reading is not critical.

Another disadvantage of the conventional wedge is its lack of symmetry which can lead to unreliable results. The thick end of the wedge must be positioned the same in the roentgen beam every time it is used if scatter in this area is to have a constant effect and reproducible results are to be obtained. Sufficient care in meeting this condition may easily be overlooked.

A new aluminum wedge

Once the limitations of the conventional stepped wedge were recognized, the design shown schematically in Fig. 1 was a logical development. This is built up from sheet aluminum stock as in the case of the usual wedge but is symmetrical about the middle step. It is not as critical with regard to positioning as earlier designs because the proportion of scattered radiation decreases gradually in going from the thickest step to the thinner steps in both directions.

If there is no systematic discrepancy between the results from the two halves of the wedge, the densities can be averaged by pairs for the

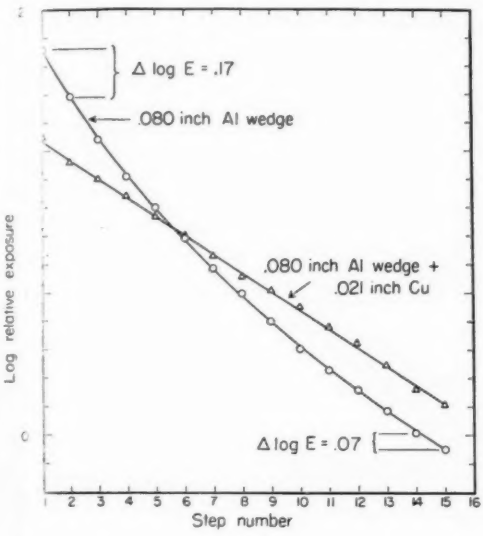
Δ log E = .17
.080 inch Al wedge
.080 inch Al wedge +
.021 inch Cu
Δ log E = .07
Log relative exposure
Step number
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16

Fig. 2. Effect of a copper filter on the attenuation curve of an aluminum stepped wedge. The location of the two curves with respect to the ordinate scale is arbitrary.

greater accuracy. If the densities are not similar, the operator should investigate his processing method to find out whether it is at fault or whether the incident roentgen beam itself is uniform over the entire area of the wedge.

A thin sheet of copper incorporated in the base of the symmetrical wedge furnishes additional absorption with very little additional scatter so that the roentgen rays transmitted are more homogeneous. Further, a simple test has shown that the copper preferentially absorbs some of the scattered radiation. Therefore, in order to take advantage of this desirable effect, the copper filter should be located in the base of the wedge. Removal of any scattered radiation tends to increase subject contrast, thus partially offsetting the reduction of contrast associated with hardening of the primary radiation by absorption. The effect of a 0.053 cm (0.021″) copper filter on the absorption curve is shown in Fig. 2. The curved line for the wedge without copper shows that the change in log exposure, or $\triangle$ log E, per step grows less as the thickness increases. With the filter added, a linear relation is obtained within the limits of experimental error.

The intensities transmitted by the various steps of a wedge depend on the wavelength distribution of the rays and therefore on the kilovoltage and kilovoltage waveform applied to the roentgen tube. A linear relation, such as that shown in Fig. 3, has been obtained with the same

wedge for 60, 70, 80, and 90 kV with a slight suggestion of nonlinear y at 60 kV. However, the slope of the line and hence the △ log E per s p decreases with increasing kilovoltages so the user must decide just l w he is going to apply the wedge. It is reasonable to expect some sim ar kilovoltage range on other roentgen machines in which linearity will e obtained within experimental limits. This suggests use of the wedge or comparing roentgen machines. Such an application might be quite us ul but the authors have not had sufficient experience to justify a discuss n.

The stepped-wedge method is adaptable to visual comparisons if he steps are separated by a constant △ log E. The film strips on wh ch the densities appear are moved parallel to each other until a matc is obtained. The logarithm of the speed ratio is then the number of st ps difference times the △ log E. Fractional steps are estimated. If a ma ch is obtained at only one point, the films differ also in contrast.

Calibration of the wedge. Anyone having experience in photographic sensitometry will be aware of the comparative simplicity of calibrating a stepped wedge. It is only necessary to make a roentgen photograph of the wedge and process it with films exposed sensitometrically (i. e. given a series of exposures whose values are accurately known). The densities of the roentgenograms are then referred to the sensitometric curve to obtain the intensity through each step. If the graph of log intensity versus step thickness is a straight line, the stepped wedge is itself suitable for sensitometric exposures. This calibration procedure is treated in detail elsewhere (CORNEY & SEEMANN). A simpler but less accurate method does not require sensitometric apparatus (KIEFFER & SEIDEMAN 1946).

Limitations of the stepped-wedge method. Conventional sensitometry of roentgen films is carried out on a time scale, i. e. the successive exposures are made for different times. Because the reciprocity law is valid for direct roentgen rays, such a series of exposures has the same relative values as if it had been made on an intensity scale; hence they may be said to represent relative intensities. In the time-scale procedure, the same quality of roentgen rays is used for all exposures; in the wedge method, the radiation quality is different because of the varying filtration from step to step. Therefore, the two methods may not agree precisely in film contrast because film varies in its sensitivity from one spectral region to another and the response at the ends of the wedge may be different from that in the middle. Similarly, relative film speeds may not be the same by the two methods because the radiation qualities cannot be identical.

Tests reported elsewhere (CORNEY & SEEMANN) as well as limited

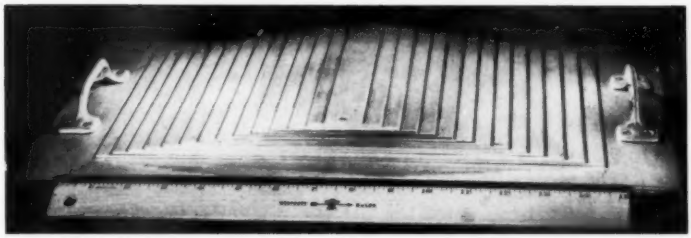

Fig. 3. Photograph of aluminum stepped wedge.

trials in connection with this investigation, have shown no great difficulties ascribable to spectral response differences even when comparing direct and screen exposures. However, such errors must exist and it is only fair to say that under some conditions they may be appreciable.

The exposure range of the aluminum wedge is about 10 and is therefore insufficient to cover, in a single exposure, what might be called the full characteristic curve of a roentgen film. This limited range is a result of filtering to attain a constant $\triangle$ log E. The thinner part of the wedge is actually made fairly thick in order to provide sufficient filtration and a limited over-all exposure range must be accepted.

A photograph of the finished wedge is shown in Fig. 3. Constructional details are given in the Appendix, p. 224.

A plastic wedge

It appeared to the authors that it is desirable to have a test object which could be used from time to time as a radiographic standard of reference to assess the performance of equipment and materials in a given laboratory, or for comparisons between different laboratories. Comparisons between test-object roentgenograms should be on a semi-quantitative basis. The roentgen ray characteristics with regard to absorption and scattering would need to be sufficiently like those of a patient so that changes in techniques would have an effect on the image of the test object comparable to that on the image of a patient. For convenience, the one test object should be usable in the range of techniques from the thinnest to the thickest patient. A plastic stepped wedge has been designed to meet these requirements.

A specific example of the need for standardized procedures in radiography is reflected in a request for assistance from the U. S. Public Health Service. The Medical Investigations Branch of the National Institute of Dental Research (N. I. D. R.), National Institute of Health

(N. I. H.), in planning an integrated long-range study of population groups, required procedures such that roentgenograms of the same patient taken over a period of years could be fairly compared. A degree of standardization was mandatory (See Public Health Rep. 1957).

To illustrate the requirements in keeping with this request, we now consider the problem as it was presented: A group of people were to be radiographed in the years 1959, 1969, and 1979, for the purpose of following developmental changes in man under varying circumstances. In view of the possible alterations in the materials and facilities for radiography over such a period of years, and in different geographical regions, the question was whether it is legitimate to compare roentgenograms produced, say, 10 years apart. It probably is not, because technical alterations may affect the appearance of roentgenograms in such a way as to render a decision of progress or retrogression of bodily conditions difficult to determine. In this particular situation, radiographic results should be similar to those obtained years before, even though techniques may actually have been improved in the meantime.

Preliminary considerations. In discussing the problem before making any attempt to design the test object, the use of realistic phantoms (SPLETTSTOSSER & SEEMANN 1955, 1957; HARRIS JR. TUDDENHAM, STANTON et coll. 1956; RODERICK 1959) was ruled out because they cannot be duplicated accurately. Furthermore, the radiographic image of a complicated structure depends rather critically on the angle of the incident roentgen rays. It is therefore difficult to decide what has happened in the technique if two images do not match perfectly.

At first thought it seemed that a stepped wedge of aluminum, as described earlier in this paper, or one of copper as described by WEIDMAN and KIEFFER 1944, would be suitable. — The copper stepped wedge of WEIDMAN and KIEFFER was fastened to the corner of cassettes which were used routinely in radiography of the chest, thus occupying an area which could be kept clear. For general use, however, and particularly in radiography of the abdomen, this would lead to the risk of having the patient's body overlie the wedge. Even if the wedge were free of overlying tissue, an indeterminate amount of scattered radiation from patients of various sizes could penetrate it and invalidate quantitative results. — The density series would depend upon exposure factors as well as upon the kind of film and its processing. An aluminum wedge was found to be more sensitive to changes in radiation quality than the pelvis, while Plexiglas plastic (polymethylmethacrylate also available under the trade name of Lucite and perhaps others) was found to have about the same sensitivity. For example, in changing from an exposure at 60 kV to one at 80 kV, the milliampere-seconds were reduced in the

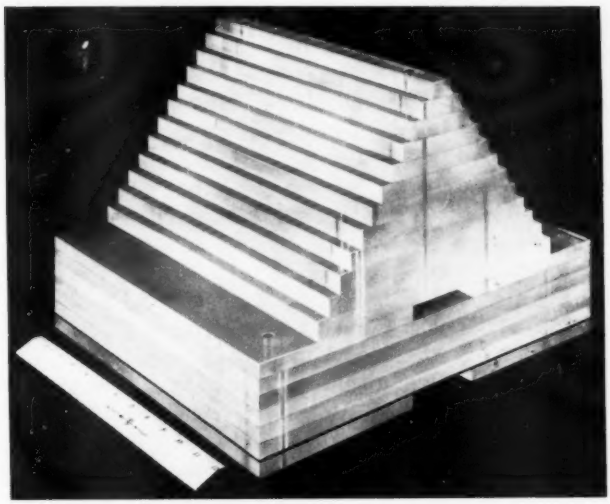

Fig. 4. Photograph of plastic stepped wedge phantom.

ratio of about 8 : 1 to maintain a constant density on a particular aluminum step. The same change in kilovolts for an antero-posterior pelvic exposure or for Plexiglas was compensated for by reducing the milliampere-seconds in the ratio of about 5 : 1. The direction of this effect is to be expected on the basis of the absorption coefficients of aluminum and tissuelike materials.

A thickness of 3.2 cm (1 1/4″) of aluminum, 16.5 cm (6 1/2″) of Plexiglas, and a medium-weight pelvis require about the same roentgen exposure. However, the ratio of scatter to primary transmitted through the aluminum is about 2 : 1 while for the other two it is about 6 : 1. Removal of scattered radiation by a Bucky grid would therefore have a greater effect on subject contrast in radiography of the tissue or Plexiglas than of aluminum. In a long-range project such as that contemplated, a change in Bucky grids may be just as probable as other changes. A resulting change in grid efficiency would have a much greater effect on roentgenograms of patients than of a metal wedge. It therefore seemed highly desirable to provide a stepped-wedge phantom whose radiographic image would be affected by the amount of scattered radiation in much the same manner as that of a patient, as well as to be affected by the other elements of technique. A stepped wedge made of a homogeneous tissuelike substance appeared to be the logical choice even though the compactness of the aluminum wedge is a very attractive feature.

The stepped wedge shown in Fig. 4 was built up of about 1.6 m (5/8") sheets of Plexiglas and has a base measuring about 35.5 × 43.2 c m. It was designed for exposure techniques commonly used for the pel ic region. An exposure for a thin patient yields a reasonable series of de si-ties at the thin end and the thickest part is about right for a techni te for the thickest patient. The effective atomic number of methylme h-acrylate is fairly close to that of water so the roentgen absorption a id scattering characteristics of this material should not be very differ nt from those of water. This is borne out by laboratory tests. Details of construction are given in the Appendix, p. 224.

It is in the interests of simplicity and convenience of use that t is phantom contains no bonelike structures. Ground bone dispersed hor o-geneously in a plastic and formed into small, stepped wedges might be located in the structure so as to occupy a part of the projected area of several of the Plexiglas steps. However, considering the fact that the practical usefulness of a device of this kind may be dependent as much on convenience as on completeness of details, it was decided to concentrate on the simpler phantom which might be used in a busy laboratory rather than one which would be discarded for lack of time to evaluate the more complete data obtained with it.

Application. Use of the stepped wedge may be visualized as follows: In the year 1959, roentgenograms are made of several patients whose measurements and type may be considered to be representative of the whole group being surveyed. If they are quite satisfactory, the identical techniques are applied in radiographing the wedge. Processing of these films is carefully controlled so as to be the same as those of the patients. All of the roentgenograms, together with pertinent data, are filed for future reference. Comparison of a patient's roentgenogram with the corresponding one of the wedge will serve for a qualitative correlation but is not essential to the method.

A few years later, say in 1969, the same group of patients are again to be radiographed. It is desirable to know beforehand whether the same nominal techniques will apply, not necessarily for the same patient, for he may have gained or lost weight, but to those having the same measurements. There is a very real possibility that changes may have occurred in equipment and materials in the intervening 10 years. Accordingly, the stepped wedge is radiographed and the films are processed exactly in accordance with the techniques which were used for the roentgenograms of the wedge made earlier. If each matches the corresponding one made in 1959, no modifications in procedure are necessary and it may be assumed that, either no changes have occurred or one change has been fortuitously compensated for by another. But if the roentgenograms of

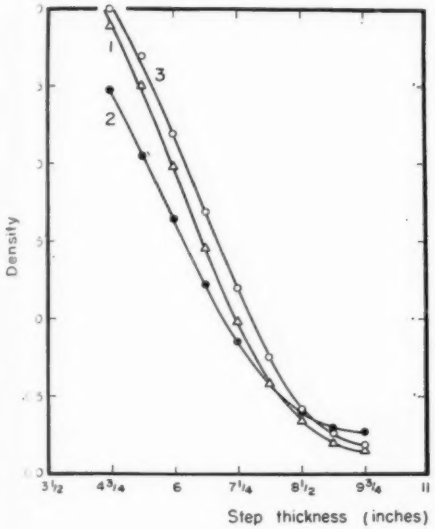

Fig. 5. Density plots from roentgenograms of the plastic (Plexiglas) stepped wedge for different techniques

Curve (1) 60 kV, 300 mAs.
Curve (2) 80 kV, 60 mAs.
Curve (3) 60 kV, 360 mAs.
An 8 : 1 Bucky grid was used in all cases.

the wedge do not match, trials must be made until they do. This is not necessarily an arduous procedure because a radiologist or qualified technician, who has been continuously associated with radiography for 10 years, will know about any significant general trends in technique, equipment or material. This knowledge will enable him to decide most quickly on the best adjustments to try.

Use of the wedge as a standard of reference has three important advantages: the wedge does not change with time as a human being may be expected to do, the appearance of the wedge roentgenogram is not as sensitive to positioning as that of a patient or a realistic phantom, and no patient need be exposed to roentgen radiation more than is necessary for his own case.

Examination of wedge roentgenograms for matching is done by cutting them down the center so as to facilitate visual comparison. Densities for the same steps must match through the useful density range. When the densities are a close match visually, they should be read on a densitometer and a curve plotted of density versus step number. Such curves offer a graphical average and are an aid in discounting minor density variations. Densities for steps of equal thickness in the same roentgenogram should be averaged. If they are not sufficiently alike to be averageable, processing or field uniformity should be checked.

No attempt has been made, in the design of the plastic stepped wedge, to obtain a linear relation between log E and thickness, as was done in the case of the aluminum wedge. Admittedly, such a relationship is desirable, for it has broader advantages than merely for film studies, but the plastic wedge was intended for use in such a variety of techniques that the exact intensity versus thickness relation was given minor consideration. The plastic wedge is simply a phantom which can be easily described and reproduced and which therefore can be used as a standard of reference for radiographic exposures.

In Fig. 5 are shown curves obtained with this wedge. Curve 1 corresponds to the exposure for a particular medical technique. Curves 2 and 3 are examples of what the same settings on different machines might perhaps yield 10 years later. What has caused the difference may not be known but it will be found that, by decreasing the milliampere-seconds in the case of Curve 3, a match for Curve 1 can be found, and, by decreasing the kilovolts *and* increasing the milliampere-seconds, Curve 2 can be moved toward Curve 1. The difference between curves (1) and (3) is not large but neither would it be large in radiographing patients. Within the limits of radiographic needs, changes in technique would be reflected in exposure and/or contrast changes in roentgenograms of the wedge.

Definition test. A definition test or tests must be included as part of the evaluation of a technique, primarily to determine whether the geometrical conditions and the quality of the intensifying screens are the same as formerly. This phase of the problem is not reported here because it has not been studied by the authors. Nevertheless, it is recognized as an essential part of the comparison of techniques.

Acknowledgement

The authors wish to express their appreciation to Dr. N. C. Leone, Chief, Medical Investigations, N. I. D. R., N. I. H., U. S. Public Health Service, who presented the problem of standardized radiographic procedures and whose continued interest has been of real assistance.

Appendix

The following notes and dimensions are intended to provide all of the information necessary for the construction of the stepped wedges described in this paper. Inasmuch as the designs are empirical, it is not known just what exceptions may be taken with the details and still retain the same performance characteristics.

Materials for aluminum wedge: Commercially pure aluminum sheet stock, ca 0.20 cm (0.[illegible]″) thick, commonly designated as 1100. Commercial stock is usually sufficiently uni[illegible]rm in thickness for the purpose of making a stepped wedge. Commercially pure co[illegible]r, 0.05 cm (0.021″) thick. Sheet lead, 0.05 cm (0.021″) thick, exact thickness not cri[illegible]al. Machine screws for assembling; cupboard door handles.

The focus-film distance for use of the aluminum wedge should be sufficient to ensure un[illegible]rmity of the roentgen field.

Materials for plastic wedge: about 1.6 cm ($^5/_8$″-thick) Plexiglas or Lucite plastic. Sh[illegible] lead, about 0.16 cm ($^1/_{16}$″) thick, exact thickness not critical. Threaded metal rod[illegible] for assembling. For convenience in handling, the wedge part is assembled as one uni[illegible] and the thick base as another. Preferably, one base-size sheet forms the base of the we[illegible]e unit so that it is easy to align with the base for exposure. One sheet in the wedge an[illegible] one in the base are partially cut out for handholes (Fig. 4).

(The sheets of the plastic wedges made by the Public Health Service were successfully cemented together by introducing chloroform between the sheets with a hypodermic needle. No threaded rods were required.)

The focus-film distance for use of the plastic wedge should be ca 1.2 m (48 ″).

	Aluminum wedge cm	Plastic wedge cm
Base	22.86 × 45.72	35.56 × 43.18
Number of steps on one side, including top step and base	38.10	33.02
Thickness of thinnest step	0.406 Al + 0.053 Cu	9.52*
Lead border,** thickness	0.053	0.159
Lead border, outside dimensions	22.86 × 45.72	35.56 × 43.18
Lead border, size of opening	9.52 × 38.10	12.70 × 36.19
Copper filter**	9.52 × 38.10 or larger	None
Increment thickness per step	0.203	1.59
Width of steps (except top)	1.27	1.27
Width of top step	2.54	2.54
Long dimension of steps	17.78	35.56

* The illustration, Fig. 4, shows 1.27 cm sheets built up to a total of 8.9 cm. The value given here, made up of 6 sheets each 1.59 cm thick, is preferred.

** These should be inserted between the two bottom sheets for mechanical protection.

SUMMARY

Two types of wedge are described, one an aluminum stepped wedge primarily for use in film studies, the other a plastic stepped wedge having absorption and scattering characteristics roughly similar to the human pelvis. The aluminum wedge has approximately exponential attenuation for a limited range of kilovolts applied to the roentgen tube, and it is a convenient device for use in film sensitometry when the highest accuracy is not required. The plastic wedge is built up of one of the commercial forms of polymethylmethacrylate (Plexiglas). The range of roentgen exposures for the pelvis is covered approximately in the thickness range of this wedge. Such a wedge has been used as a standard of reference for radiographic techniques under field conditions with a considerable degree of success in epidemiologic studies.

[illegible]–603088. *Acta Radiologica. Vol. 53.*

ZUSAMMENFASSUNG

Es werden zwei Arten von Keilfiltern beschrieben: ein stufenförmiger Keil aus Aluminium zur Verwendung bei Filmstudien sowie ein Keil aus Plast mit Strahlen absorbierenden und -zerstreuenden Eigenschaften, die ungefähr denen des menschlichen Beckens entsprechen. Der Aluminiumkeil bewirkt eine Abschwächung der Exponierung für einen bestimmten Kilovoltbereich und stellt ein geeignetes Mittel zur groben Messung der Filmempfindlichkeit dar. Der Plastkeil besteht aus einer handelsüblichen Form von Polymethylmethacrylat (Plexiglas). Das Ausmass der Strahlendurchlässigkeit des Beckens entspricht dem Dickenmass des Keiles. Dieser Keil wurde als radiographische Standardmethode unter einfachen Bedingungen bei epidemiologischen Untersuchungen mit beachtenswertem Erfolg angewendet.

RÉSUMÉ

Les auteurs décrivent deux types de coins, l'un à gradins, en aluminium, primitivement destiné à l'étude des films, l'autre à gradins, en plastique, présentant des caractéristiques d'absorption et de diffusion à peu près semblables à celles du bassin humain. Le coin d'aluminium a une atténuation approximativement exponentielle pour une gamme limitée de tension appliquée au tube, et convient pour la sensitométrie des films quand une haute précision n'est pas nécessaire. Le coin de plastique est fait d'une des formes commerciales du polyméthylméthacrylate (Plexiglas). La gamme des facteurs d'exposition pour le bassin est approximativement couverte par la gamme d'épaisseur de ce coin. Un coin de ce type a été utilisé, avec de bons résultats, comme étalon de référence pour les techniques radiographiques dans des conditions simples, en vue d'études systématiques de populations.

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FROM THE RADIUM CENTRE (DIRECTOR: PROF. JENS NIELSEN), AND THE DEPARTMENT OF RADIOPHYSICS (DIRECTOR: J. AMBROSEN), COPENHAGEN, DENMARK

WEDGE FILTERS IN ROENTGEN THERAPY OF CARCINOMA OF THE LARYNX AND HYPOPHARYNX

by

Sigvard Kaae and *Niels Brene*

The use of wedge filters to obtain a uniform dose distribution in tumours fairly close to the skin and down to a depth of 5 to 10 cm was described in 1944 by ELLIS & MILLER who used the technique in treating lesions of the maxillary antrum and the floor of the mouth. This technique was introduced at our Radium Centre towards the end of 1957 when the necessary physical and technical assistance had become available. It has been employed particularly in the treatment of tumours of the head and neck.

It is important to obtain a fairly uniform dose over a growth. Outside this area, the dose should be as low as possible to avoid unnecessary damage to healthy tissue and to keep the integral dose low.

We used, up till the end of 1957, two opposed lateral fields in roentgen therapy of the larynx. This gives a somewhat smaller dose to the tumour than to the skin and a somewhat higher dose to the anterior than to the posterior part of the larynx.

By a multi-field technique (without a wedge filter) a fairly homogeneous radiation is obtained over a tumour when the angles between the field directions are made equal and the contribution of each field to the tumour dose is the same (PATERSON). This may be accomplished in carcinoma of the larynx by one anterior field and two posterior oblique

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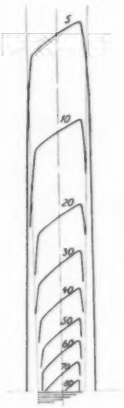

Fig. 1. Isodose curves for a 2 cm² field with 45° wedge filter, figures indicating percentages of surface dose when using applicator without wedge filter.

Fig. 2. Set-up for roentgen irradiation of left field in carcinoma of the larynx, with treatment cell, wedge filter, 2 cm² field, and back pointer.

fields with 120° between their directions. The anterior field gives a short skin-tumour distance and the two postero-lateral fields rather long skin-tumour distances. It is necessary, therefore, to apply a higher skin dose to the two postero-lateral fields, and this involves a considerable irradiation of normal tissue outside the tumour as well as a higher integral dose.

Technique

Wedge filters enable a uniform tumour dose to be obtained by using only fields with short skin-tumour distances. This affords less irradiation of the surrounding healthy tissue and a lower integral dose than the multi-field technique without wedge filters.

Accurate data about the dose distribution in each field are required in order to utilize the wedge-filter technique to the full and are most easily obtained by isodose curves. To this end, we measured isodose curves by means of an isodose plotter in a water phantom for a number of different field sizes down to 2 cm² with wedge filters corresponding to slopes of 0°, 30°, 45°, and 60° (0° slope being for a field without wedge filter). The surface dose could not be measured owing to the thickness of the wall of the water phantom so that isodose curves for the applicator without wedge filter were standardized at a point on the central axis from published depth dose data. All isodose curves for this applicator were plotted without altering the standardization, so that all the percentage depth doses are in terms of 100 % surface dose for the applicator without wedge filter (Fig. 1). Factors: 250 kV, HVL 3.2 mm Cu, and FSD 50 cm. The wedges were made of thin copper sheets.

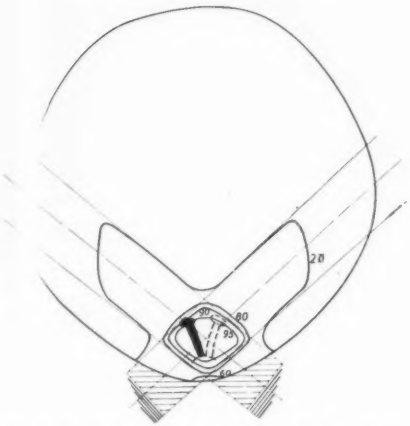

Fig. 3. Carcinoma of right vocal cord. Two fields of 2 cm², 45° wedge filter.

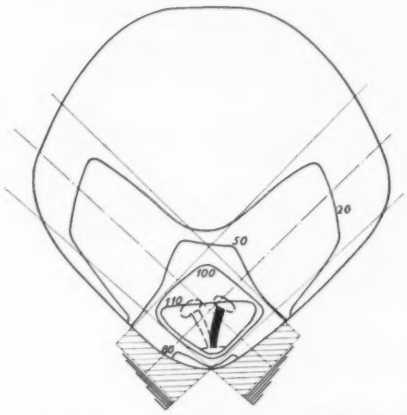

Fig. 4. Carcinoma of left vocal cord. Two fields of 3 cm², 45° wedge filter.

Black portions indicate tumour and striped sections wax.

Treatment shell. Small fields have to be used in order to reduce the irradiation of the surrounding normal tissue as far as possible. This presupposes an extremely accurate set-up technique obtainable by using a treatment shell and back pointer. The shell is made of thermoplastic material (cellulose acetate), a sheet about 1 mm thick being moulded over a plaster cast of the patient. The outline of the neck at the tumour level is drawn on paper, the tumour area is marked, and the field sizes and accurate field directions are estimated by means of isodose curves. Paraffin wax blocks are built upon the shells to determine the position of the applicator and to fill any gaps with tissue equivalent material. The positions of the fields are checked by roentgen films using the shell for beam direction, and when correct fields have been obtained the wedge filters are fitted on the wax blocks. The radiation is administered each time with the treatment shell in situ (Fig. 2).

Treatment

Carcinoma of the true vocal cords of Stage I and II according to the classification of NIELSEN & STRANDBERG was treated after the introduction of the wedge-filter technique by small fields, which were first 3 cm square and later 2 cm square (Figs. 3 and 4). This affords a tumour dose about 20 % in excess of the maximum skin dose, with a very rapid

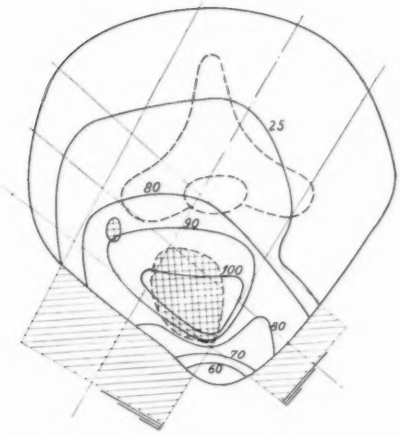

Fig. 5. Carcinoma of right side of epiglottis, right lateral wall of hypopharynx, right false vocal cord, and probable node metastasis on right side of neck. Oblique right field: 5 × 6 cm; oblique left field: 3 × 6 cm, both with wedge filters of 45°.

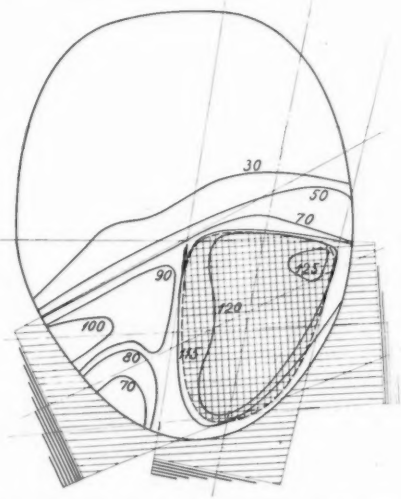

Fig. 6. Widespread carcinoma of left piriform sinus, inoperable because of advanced age. Right field: 5 × 6 cm, wedge filter 60°; anterior field: 4 × 6 cm, wedge filter 30°; left field: 5 × 6 cm, wedge filter 30°.

Checked sections indicate tumour and striped sections wax.

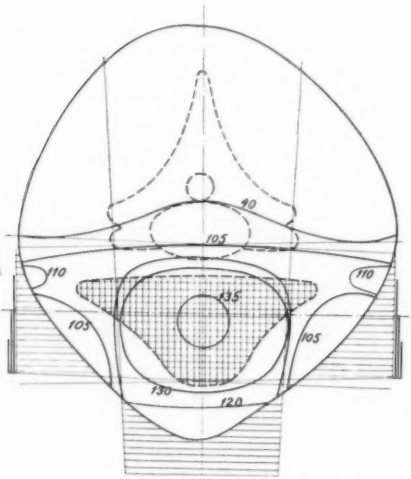

Fig. 7. Carcinoma of epiglottis; probable node metastases on both sides of neck. Anterior field: 5 × 8 cm, no wedge filter; lateral fields: 4 × 8 cm, modified wedge filter.

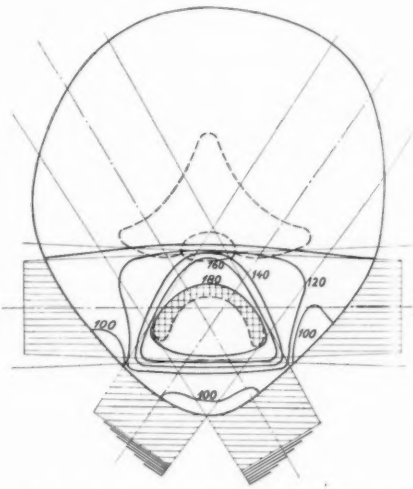

Fig. 8. Carcinoma affecting posterior and lateral walls of hypopharynx. Lateral fields: 3 × 5 cm, no wedge filter; oblique fields: 3 × 5 cm, wedge filter 60°.

de ease in the dosage outside the tumour area and without hot spots. Tl use of small fields gives maximum irradiation only of a small area of ıe mucous membrane of the larynx and hypopharynx.

Since the introduction of this technique, 13 small larynx cancers have be ı treated with 3 cm² fields and 8 with 2 cm² fields. The tumour dose a treatment period varied according to the mucous reactions. The p ıary result has been good in all these cases. The tumours have com- pl ely disappeared, with moderate mucosal reactions, only very slight d skin reactions and satisfactory end-function. Preliminary clinical e: erience indicates that 2 cm² fields are sufficient. It is too early to m ke any comment on the late results, and nothing definite can be sa regarding a suitable tumour dose or treatment period.

More widespread carcinomas of the larynx and carcinomas of the hypo- ph rynx have been treated by the same technique, but with larger fields to orrespond to the extent of the growth. The treatment had as a rule to be extended to lymph node metastases or areas where metastases pr bably lay. It may be advantageous in such cases to employ 3 or 4 fie ds, 2 or more of them with wedge filters (Figs. 5, 6, 7, and 8). Telecobalt th rapy was used, however, in some of these cases in order to reduce the ris of cartilage necrosis. The technique was otherwise the same and a wedge filter, treatment shell, and back pointer were employed; portals were however cut out in the treatment shell in place of the paraffin wax blocks, in order to maintain the lower surface dose of cobalt radiation on the skin.

SUMMARY

Roentgen irradiation of laryngeal and hypopharyngeal carcinoma with a wedge filter, treatment shell, and 'back pointer' is described. Special attention has been paid to the use of small fields, 2 cm², in connection with this technique in the treatment of small carcinomas of the vocal cords.

ZUSAMMENFASSUNG

Röntgenbestrahlung von Larynx- und Hypopharynxcancer unter Verwendung von Keilfilter, Behandlungsschale und 'back pointer', wird beschrieben. Im Zusammenhang mit dieser Technik wurde bei der Behandlung kleiner Stimmbandkarzinome der Verwendung kleiner Felder, 2 cm², besondere Aufmerksamkeit gewidmet.

RÉSUMÉ

Les auteurs décrivent la roentgenthérapie du cancer du larynx et de l'hypopharynx avec un filtre en coin, une coquille de traitement et un rétrocentreur. Ils ont particulièrement étudié l'utilisation de petits champs, 2 cm², avec cette technique pour le traitement de petits cancers des cordes vocales.

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FROM THE DEPARTMENTS OF RADIOTHERAPEUTICS (DIRECTOR: PROF. J. S. MITCHELL) AND VETERINARY ANATOMY (PROF. J. D. BOYD), UNIVERSITY OF CAMBRIDGE, ENGLAND

QUANTITATIVE MEASUREMENTS OF OXYGEN TENSION IN NORMAL TISSUES AND IN THE TUMOURS OF PATIENTS BEFORE AND AFTER RADIOTHERAPY

by

Donald B. Cater and *Ian A. Silver*

The importance of oxygen tension to radiosensitivity is now a well recognized fact. HOLLCROFT, LORENZ and MATHEWS (1952) and GRAY, CONGER, EBERT, HORNSEY and SCOTT (1953) refocussed attention on the earlier findings of CRABTREE and CRAMER (1933) and MOTTRAM (1935 and 1936). GRAY et coll. showed that the sensitivity of tumour cells to roentgen rays was about three times as great when they were irradiated in a well oxygenated medium as under anoxic conditions, a figure closely comparable with that found by other workers for plant and insect tissues. The rationale of the use of oxygen in radiotherapy is that it might increase the oxygen tension of anoxic parts of the tumour and make these as sensitive to radiation as the well oxygenated parts and thus might increase the cure rate. GRAY (1957) has reviewed the radiobiology of the oxygen effect, and MITCHELL (1957 a) has used oxygen administered at atmospheric pressure as a radiosensitizer in radiotherapy either alone or in combination with injections of Synkavit (tetrasodium 2-methyl-1: 4 naphthohydroquinone diphosphate) since 1953. CHURCHILL-DAVIDSON,

Submitted for publication 25 April 1959.

FOSTER, THOMLINSON, FLEMING and PAINE (1958) have treated a numb r of patients with radiation and oxygen at a pressure of 3 or 4 atmo - pheres. It is clear that if oxygen is to be used as a radiosensitizer in a rational manner it is important to know the oxygen tension of tumo r and normal tissues and the change of oxygen tension which occurs wh n oxygen is breathed. Our experience with the use of the oxygen-catho e of DANNEEL (1897—98) for following changes in oxygen tension in vi o (CATER, PHILLIPS and SILVER 1957a, b, c) encouraged us to ada t the method for quantitative measurements (CATER, SILVER and WILSO , 1959). Using this technique, quantitative measurements of oxygen te - sion have been made in tumours of patients before and after completi g a course of radiotherapy, and in muscle, subcutaneous tissue and bo e marrow of normal subjects when breathing air and when breathi g oxygen at atmospheric pressure. (See CATER 1957, 1958, 1959 and CAT R and SILVER 1958 for preliminary reports.)

Materials and methods

The modification of the oxygen-cathode method was that described by CATER, SILVER and WILSON (1959). The electrodes were made from platinum or gold wire of 315 μ diameter, insulated with 'Araldite 985 E' and the end ground with a fine hone to form a flush-ended electrode. The electrodes were sterilized by boiling in distilled water. Four electrodes were inserted into tumour or normal tissue to obtain a fair sample. The skin was anaesthetised and the electrodes inserted by means of a hypodermic needle, 2 cm of which had been ground to produce a U-shaped section. This needle was inserted and the electrode run along the groove, the needle was then withdrawn leaving the electrode in position. The circuit was completed by a reference electrode consisting of a silver wire insulated with Aradite except at its tip which was coated with silver chloride deposited by electrolysis. The silver/silver chloride electrode was sterilized and inserted subcutaneously into a convenient site. It was important to insulate the patient carefully from earth by perspex blocks under the legs of the operating table and a sheet of perspex between the patient and the operating table. The electrodes were connected by concentric cables to a 4-channel switch with rhodium-plated contacts. This allowed any one of the 4 electrodes to be connected at will to the amplifier. A negative potential of 0.6 V compared with the Ag/AgCl electrode was placed on the platinum or gold electrodes and the catalytic reduction of the oxygen which diffused on to the electrode produced a current of about 1×10^{-9} amp per 1 mm Hg pressure of oxygen. This current was amplified by a circuit consisting of an electrometer valve (ET3) and three transistors. There was 100 % negative feed back to give stability and the current was read on a microammeter. The apparatus is light, portable, robust, and convenient for clinical use. Electrodes of the size used took a few minutes to give a steady reading and after these were obtained the patient was given oxygen to breathe through a polythene mask (7 l/min) for 10 minutes. Readings were taken every 15 second, i. e. one reading per minute on each of 4 electrodes. The electrodes were calibrated in an artificial extracellular fluid which had been bubbled with an air/5 % CO_2 mixture and corrections made for temperature and barometric pressure. The readings obtained in the patients were reduced to oxygen tension from the calibration values and the results plotted against

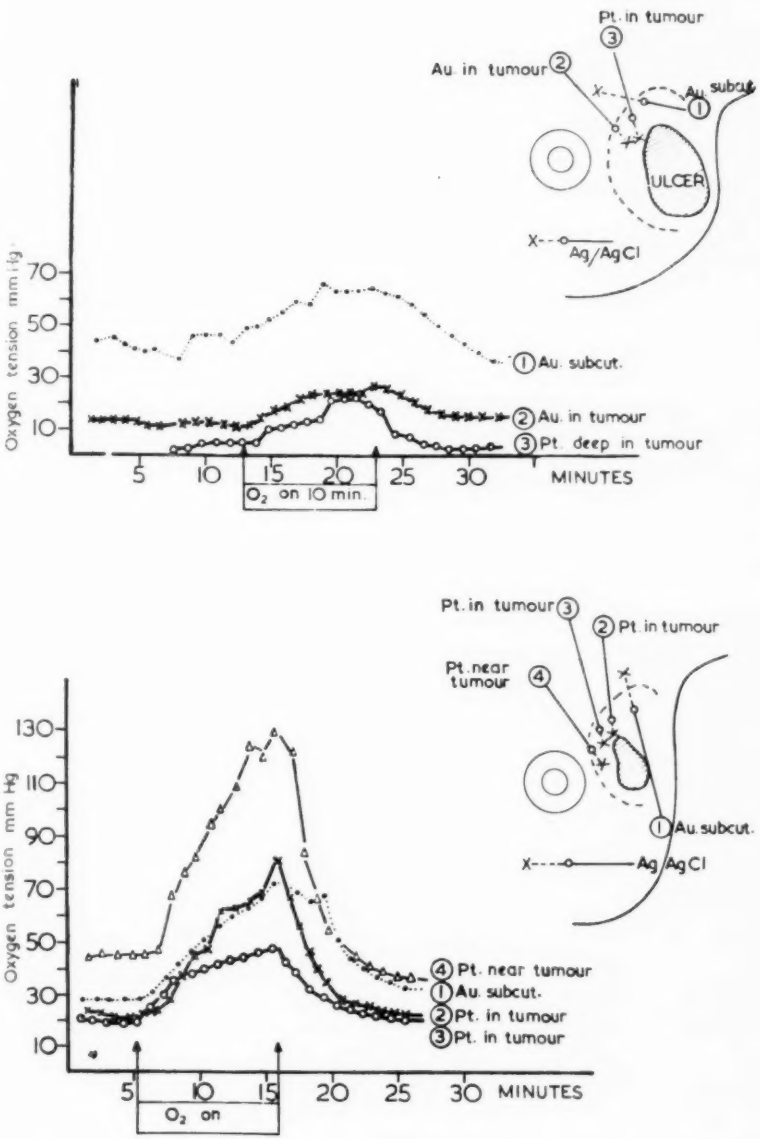


Fig. 1. Case 1. Upper tracing shows the oxygen tension in an ulcerated mammary carcinoma before radiotherapy, and the lower tracing after the completion of radiotherapy.

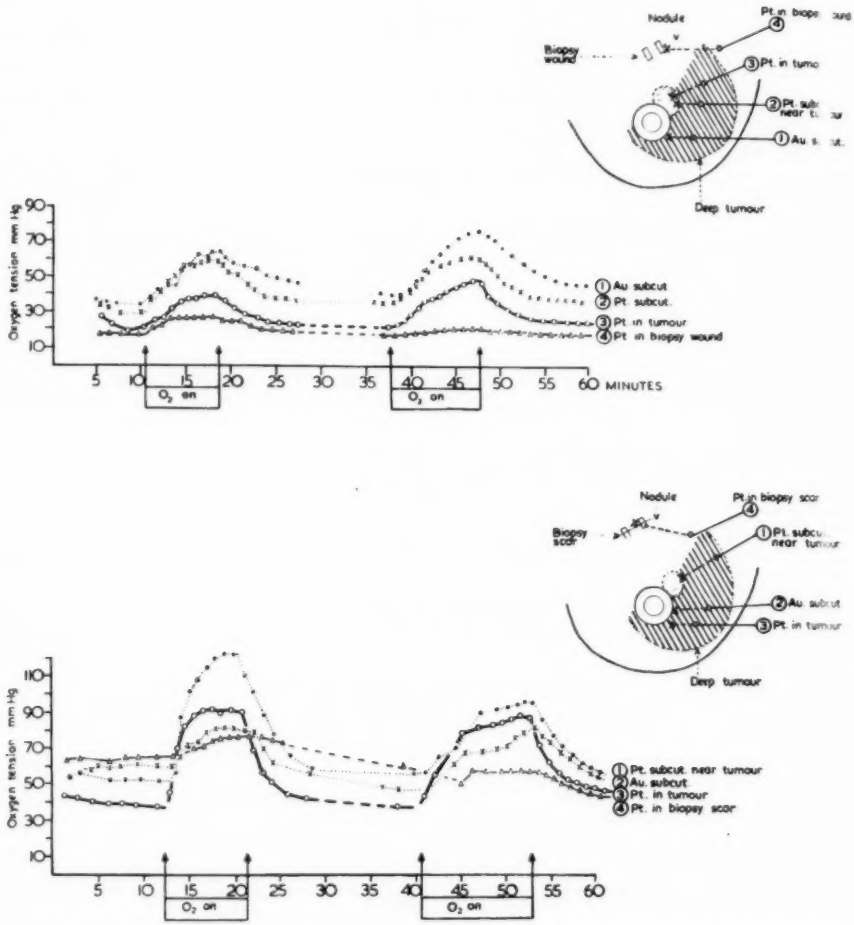
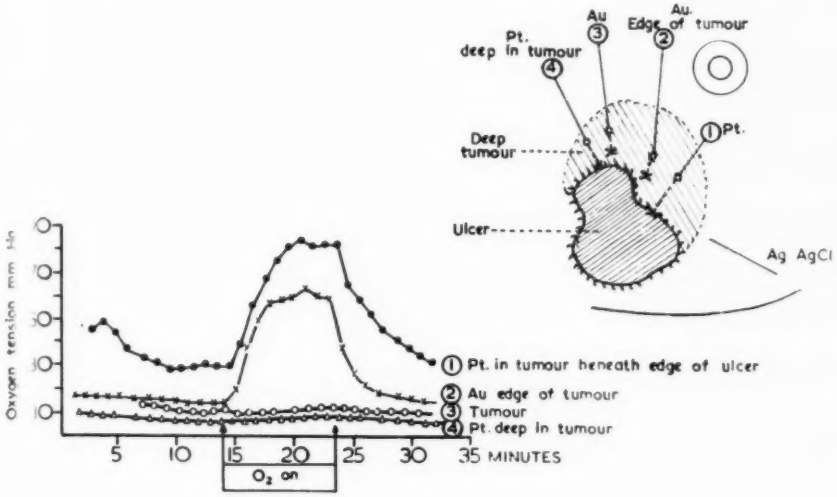


Fig. 2. Case 2. Upper tracing shows the oxygen tension in a mammary carcinoma 3 days after treatment had begun, lower tracing after completion of radiotherapy.

time on graph paper. In patients, observations were made before commencing treatment and again immediately after completing the course of radiotherapy. Normal volunteers were also used for some of the measurements of oxygen tension in muscle, subcutaneous tissue and bone marrow. A special electrode was used for bone marrow; the gold wire insulated with Araldite was incorporated into the trephine part of a bone marrow biopsy needle.



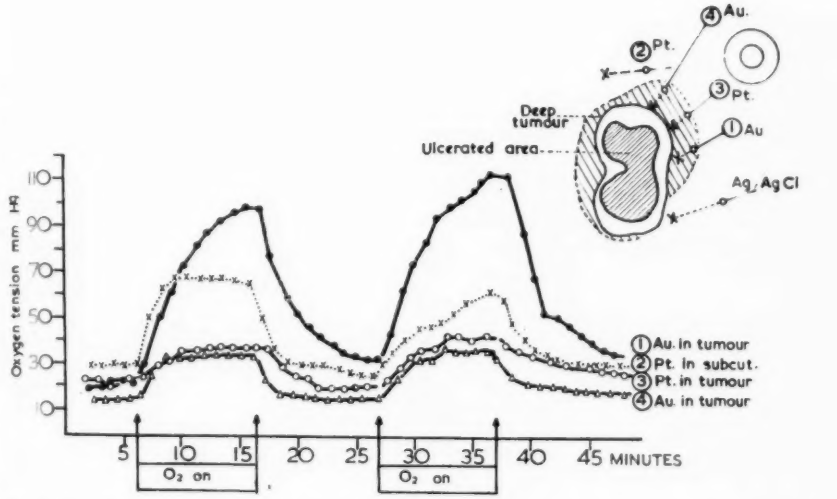


Fig. 3. Case 3. Upper tracing shows the oxygen tension in an ulcerated mammary carcinoma before treatment, lower tracing after completion of radiotherapy.

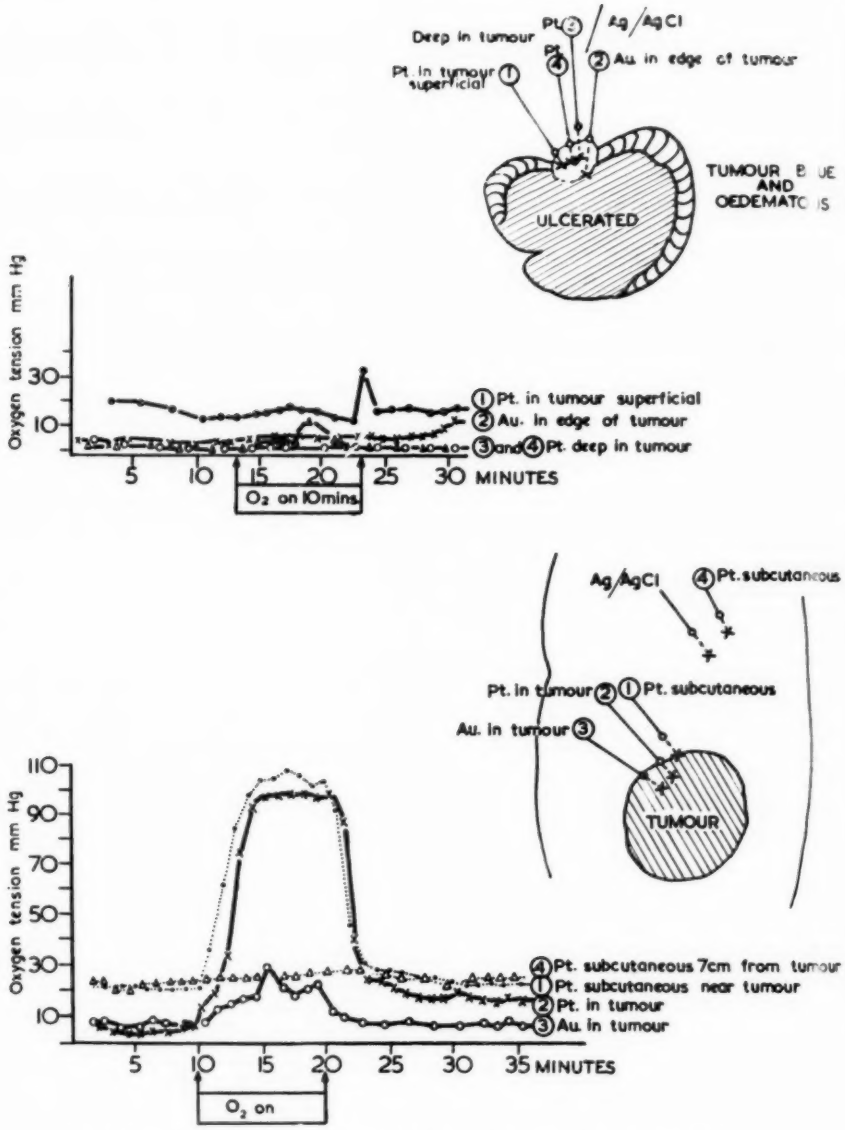


Fig. 4. Case 4. Upper tracing before radiotherapy and lower tracing after radiotherapy.

Results

The patients selected for investigation had superficial tumours suitable for the insertion of electrodes. No attempt was made to choose patients who were likely to respond favourably to treatment. A large proportion of the cases had very advanced and ulcerated lesions.

Case 1. Mrs. E. D. R., aged 74, had an ulcerated carcinoma-stage III of the left breast, present for at least 6 months. Fig. 1 shows the resting levels of tumour oxygen tension, and the response to breathing oxygen, both before and after radiotherapy (minimum tumour roentgen dose of 250 kV was 3 255 r and the maximum skin dose 4 0 r delivered in 18 days). Both the resting level and the oxygen response were raised after treatment. The tissue near the tumour was obviously affected by the radiation and showed a large increase of oxygen tension when oxygen was breathed following the completion of treatment. There was a good immediate clinical response to treatment but the tumour recurred 4 months later.

Case 2. (Fig. 2). Mrs. V. E. E., aged 58, carcinoma of the left breast with a 2 years history; the upper record was made after the tumour had received a total of 434 r, in 2 doses on the previous 2 days. The lower record was made on the same day as the final treatment after a total minimum tumour dose of 3 975 r delivered in 22 days. The tumour oxygen tension showed an increased response to the breathing of oxygen after radiotherapy. It is interesting to note that the area of the biopsy wound was relatively insensitive to the administration of oxygen both at the beginning and end of treatment although the resting level was much higher after treatment.

Case 3 (Fig. 3). Mrs. A. E. P. L., aged 50, with a large fungating carcinoma of the left breast and a 2 years history. The upper record was made before treatment started and shows little or no change in oxygen tension on the two electrodes in tumour when oxygen was breathed. It may be significant that the two sites showing a marked rise of oxygen tension are at the vascular edge of the ulcer and the edge of the tumour. Following radiotherapy over 22 days (M. T. D. 2 500 r, S. D. 2 840 r) and aureomycin locally to the ulcer, the electrodes were replaced in the lesion and the recordings from them show some increase in the resting level of oxygen tension in the lesion and an augmented response to the breathing of oxygen.

Case 4 (Fig. 4). Mrs. T. F. B., aged 81, with an oedematous, cyanosed, fungating and ulcerated growth on the right arm, present for 7 months. This was probably a metastatic deposit from a mammary carcinoma. The upper record taken before treatment shows an exceedingly low oxygen tension and little or no change when oxygen was breathed, as might have been predicted from the clinical appearance of the lesion. The lower record was made the day following completion of radiotherapy (M. T. D. 2 499 r, S. D. 2 480 r in 9 days plus 1 050 r to the fungating mass). The tumour was red in colour and much smaller. The resting levels of oxygen tension in the tumour were higher and there was a good response to the breathing of oxygen. The gold electrode in subcutaneous tissue outside the treatment area showed a normal resting level but no response when oxygen was breathed, which suggested that it was embedded in subcutaneous fat. The initial response to treatment was good and the lesion healed. There was a recurrence at the edge of the treated area the following year.

Case 5 (Fig. 5). Mr. C. S., aged 76, with a large raised squamous cell carcinoma of the dorsum of the right hand; a typical malignant ulcer, recurring after excision. The upper

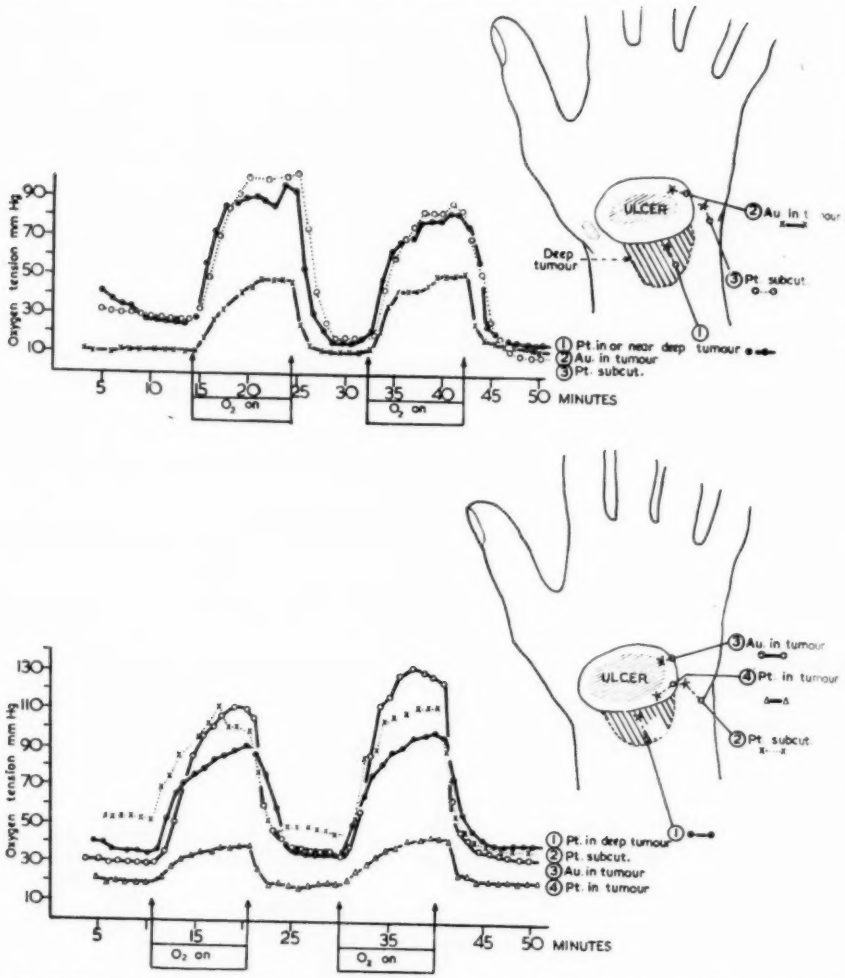


Fig. 5. Case 5. Upper tracing shows the oxygen tension in an ulcerated squamous cell carcinoma four days before treatment, and lower tracing after treatment.

record was taken four days before treatment with Ir^{192} teletherapy (M. T. D. 4 620, S. D. 5 201 delivered in 8 days). The lower record was made 12 days later immediately after the last treatment. It will be noticed that the resting levels of oxygen tension and the response to breathing oxygen were high both before and after treatment. There is only a slight increase after irradiation. The high oxygen tension in ulcerated infected epithelioma is probably due to the inflammatory reaction and good vascular supply, (see also Fig. 9). This may be one of the factors in the favourable response to radiation which is usually found with this type of tumour.

Analysis of oxygen tension in tissues

In all, fifty-one experiments were performed, twenty on normal volunteers, twenty-four on patients with cancer and seven on patients with leukaemia or anaemia. Ten of the cancer patients were examined before and after treatment. The pooled data from readings on electrodes in normal muscle, subcutaneous tissue and bone marrow, and in or near tumour tissue before and after treatment are shown in the Table on pp. 242—243.

In column 4 of this table it can be seen that the oxygen tension in muscle when air was breathed was rather low but there was some response to breathing oxygen (column 6). The oxygen tension in subcutaneous tissue was considerably higher and the response to breathing oxygen correspondingly greater. On the other hand the oxygen tension in normal bone marrow changed very little when oxygen was breathed. In tumours before radiotherapy the oxygen tension was usually low and rose only slightly when oxygen was breathed, but after radiotherapy oxygen tension was generally higher and responded briskly when oxygen was breathed by the patient.

Statistical analysis of the results shows that the log oxygen tension has a normal distribution. This type of variation may be due to the position of the electrode in the tissue with respect to the capillary blood vessels even though the electrode is large enough to be influenced by more than one capillary. Mean values of oxygen tension differ little from those given in the provisional report of CATER and SILVER (1958) but the log distribution makes the 95 % confidence limits for these means rather large. (Columns 5 and 7 of the table.) It was noted however that those electrodes which gave a high-reading when the subject breathed air gave a correspondingly higher reading when oxygen was breathed and vice versa, so that the ratio of the readings when oxygen had been breathed for ten minutes, divided by the readings when air was breathed, is a constant, K, of mean value 2.1 to 2.3 for muscle, subcutaneous tissue, untreated tumour and tissue near tumour (column 8). After radiotherapy this constant was significantly greater for tumour (2.93), but not for irradiated tissue near tumour (2.26). Tensing a muscle when breathing air gave a similar increase of oxygen tension to that which occurred when oxygen was breathed with muscle at rest.

Oxygen tension in normal bone marrow was rather low and there was little or no increase when oxygen was breathed ($K = 1.33$ which does not differ significantly from one). The position of the electrode in bone marrow was checked in every case by a smear from the specimen removed by the trephine, and by aspiration-biopsy when the electrode was withdrawn.

Table

Analysis of pooled data of oxygen tension in the tissues of patients and normal subjects

1	2	3	4
Tissue	Number of subjects	Number of readings breathing air and oxygen	Mean O_2 tension when subject was breathing air
Muscle	17	23	14.3
Subcutaneous, normal subjects	17	24	42.0
Tumours before radiotherapy	10	26	17.7
Tumours after radiotherapy	10	23	27.3
Tissue near tumour before radiotherapy	10	12	23.0
Tissue near tumour after radiotherapy	10	15	39.9
Normal bone marrow	14	15	15.5
Bone marrow in leukaemia and anaemia	7	7	

To date seven patients with leukaemias or anaemias have been investigated in collaboration with Dr. J. WOODLIFF. High values of oxygen tension in bone marrow when breathing air, and a big response to breathing oxygen, have been observed in some of these cases but the numbers are too small for analysis. It is proposed to publish observations on abnormal bone marrow when we have amassed sufficient data, but mention is made of the preliminary findings here because they indicate that electrodes in bone marrow are capable of giving high values and this gives us confidence that the low readings and poor response to breathing oxygen in normal marrow were probably real and not an artefact. The findings suggest that the use of oxygen as a radiosensitizer is unlikely to increase radiation damage to normal bone marrow.

Effect of Synkavit on oxygen tension

Case 6 (Fig. 6). Miss F. E. F., aged 34, with a mammary carcinoma was being treated with intravenous Synkavit and 250 kV roentgen. On the eighth day of treatment after a dose of 1 182 r had been given, electrodes were inserted into the tumour and a record of oxygen tension was taken when oxygen was breathed for 45 minutes. 75 mg Synkavit was injected intravenously when the oxygen tension in the tumour appeared to be maximal. The Synkavit had no dramatic effect on the oxygen tension, but it may have been responsible for the slow rise in tension which followed the injection. This patient gave a very good clinical response at completion of treatment (tumour dose 3 657 r with 1 175 mg Synkavit in 28 days).

5	6	7	8	9
95 % confidence limits	Mean O_2 tension when subject was breathing oxygen	95 % confidence limits	Mean ratio of electrode readings: When breating oxygen / When breathing air	95 % confidence limits of mean
9.5 to 21.4	27.5	18.1 to 41.9	2.07	1.70 to 2.51
2.9 to 53.5	78.3	64.5 to 95.1	2.28	1.74 to 2.98
2.3 to 25.5	34.7	23.3 to 51.7	2.06	1.71 to 2.48
9.1 to 39.0	65.1	47.8 to 88.7	2.93	2.29 to 3.76
8.2 to 29.0	52.5	35.1 to 78.5	2.27	1.68 to 3.24
3.4 to 45.5	81.8	70.0 to 95.7	2.26	1.74 to 2.93
9.2 to 26.1	17.9	9.2 to 34.7	1.33	0.98 to 1.80
			3.38	1.57 to 7.28

Case 7 (Fig. 7). Mrs. G. I. H., aged 43, with a carcinoma of breast of two years standing: clinical stage IV. Records of oxygen tension were made before and after treatment with radiotherapy and intravenous Synkavit. Synkavit had little or no effect on the oxygen tension of the tumour either before or after treatment. The second tracing shows the typical increase in resting oxygen tension seen after radiotherapy (M. T. D. 3 250 r + 985 mg Synkavit I. V. in 18 days). The immediate response to treatment was satisfactory but there was early recurrence of the tumour.

Case 8 (Fig. 8). Mrs. L. M. L., aged 63, had an ulcerated carcinoma of breast, stage IV. The records and changes of oxygen tension are very similar to those in Fig. 7, both before and after treatment. The Synkavit injection after treatment was followed by a slight transient fall in oxygen tension which was probably due to alteration of the patient's respiration. In this patient Synkavit produced feelings of nausea. The record quickly returned to its former level and this was followed by a slow rise in oxygen tension as was seen in the two previous records. It can be seen quite clearly from these three records that Synkavit does not alter oxygen tension in tumours significantly either immediately or up to 30 minutes after injection.

Effect of diathermy on oxygen tension

Case 9 (Fig 9). Mr. J. C., aged 74. The tumour was an epithelioma on the dorsum of the left wrist. This lesion, like the one represented in Fig. 5, was rather vascular and ulcerated. Electrodes in the tumour recorded considerable increase in oxygen tension when oxygen was breathed. Diathermy plates were then placed so that minimal heating of the electrodes would occur and the recording apparatus was disconnected when the diathermy was switched on. This was necessary as the recording apparatus was sensitive

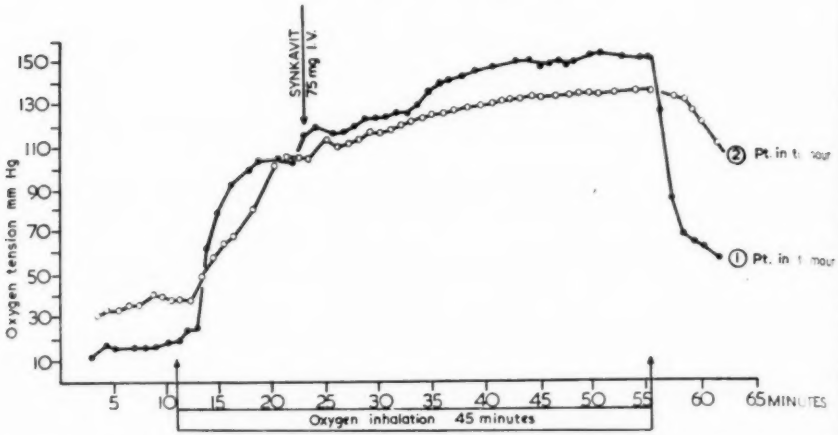


Fig. 6. Case 6. The changes of oxygen tension in a mammary carcinoma during inhalation of oxygen and intravenous injection of 75 mg Synkavit. The observations were made on the 8th day of treatment.

to the short-wave radiation of the diathermy apparatus. One set of readings was made immediately the diathermy apparatus was switched off when the patient was breathing air, and then the diathermy was applied with the patient breathing oxygen and a record taken immediately the diathermy was switched off with the patient still breathing oxygen. It can be seen that when air was breathed there was a tendency for the oxygen tension to fall slightly after diathermy, and when oxygen was breathed the increase of oxygen tension was considerably less than before diathermy. Also after returning to breathing air the oxygen tension fell below the original resting level in the tumour. The electrode in subcutaneous tissue well away from the diathermy field was unaffected. There was certainly no suggestion in this experiment that diathermy had increased the oxygen tension in the tumour, on the contrary there was every indication that it had decreased it.

The effect of general body heating on oxygen tension was observed in an anaesthetised rat which accidentally became hyperthermic (44° C) due to an external source of heat. As in the case of local heating by diathermy, the oxygen tension in muscle and subcutaneous tissue in the hyperthermic rat fell considerably below the levels seen at normal body temperature although the respiratory rate was greatly increased.

Miscellaneous observations

Electrodes were placed in a secondary deposit from a malignant melanoma after treatment with roentgen and a course of nitrogen mustard oxide injections. The tumour showed a relatively high resting level of oxygen tension and a good response when oxygen was breathed. An injection of Nitromin was without obvious effect upon the oxygen tension.

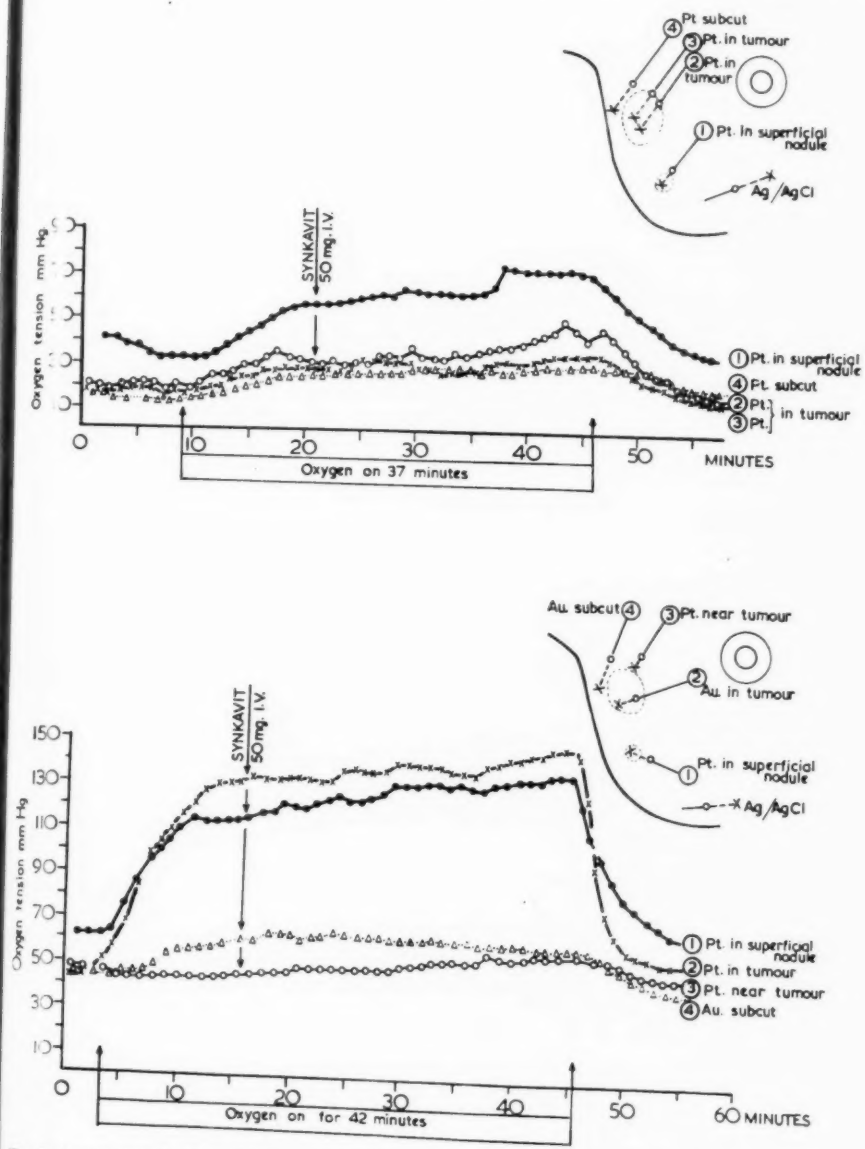


Fig. 7. Case 7. Effect of breathing oxygen and intravenous injection of Synkavit on the oxygen tension in a mammary carcinoma. Upper tracing before treatment, and lower tracing after radiotherapy.

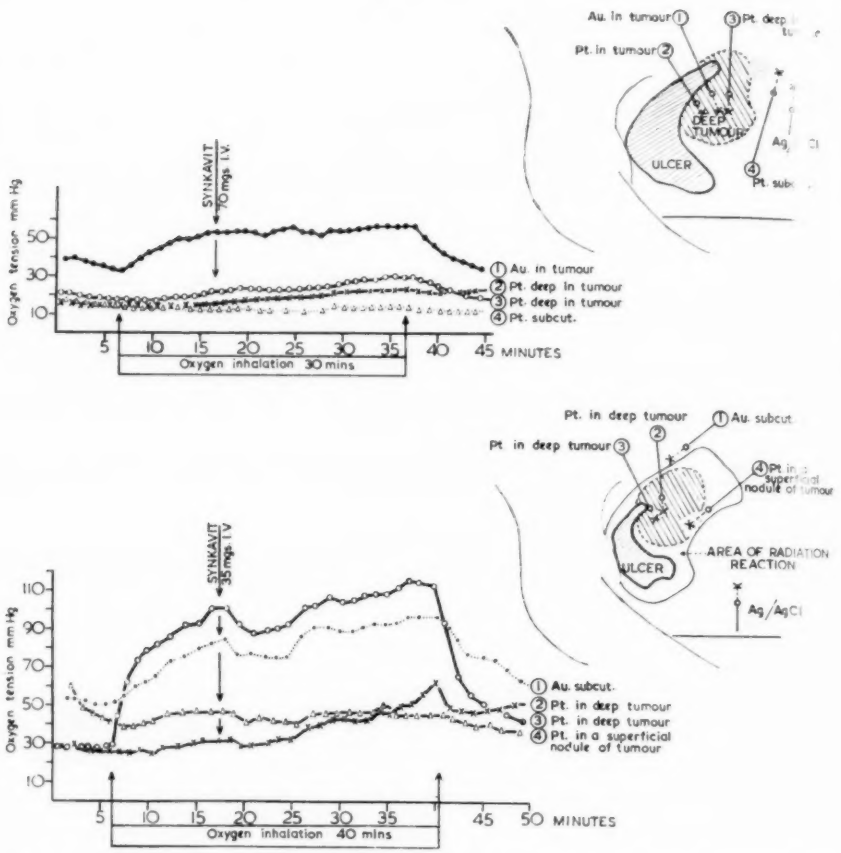


Fig. 8. Case 8. Effect of breathing oxygen and intravenous injection of Synkavit on the oxygen tension in an ulcerated mammary carcinoma. Upper tracing before treatment and lower after radiotherapy.

Case 10 (Fig. 10). Mrs. S. E. M., aged 62. A case of reticulosis of the lymph nodes of the neck. Electrodes inserted into one of the affected lymph nodes before treatment showed a high resting level of oxygen tension and a good response when oxygen was breathed. After treatment (T. D. 1 350 r, of 250 kV roentgen during 14 days) there was a dramatic retrogression of the affected nodes to such an extent that it was considered inadvisable to insert electrodes when treatment was completed.

It was noted in the small number of anaemia cases investigated that normal levels of oxygen tension in muscle and subcutaneous tissue were low but some very big responses to breathing oxygen were obtained.

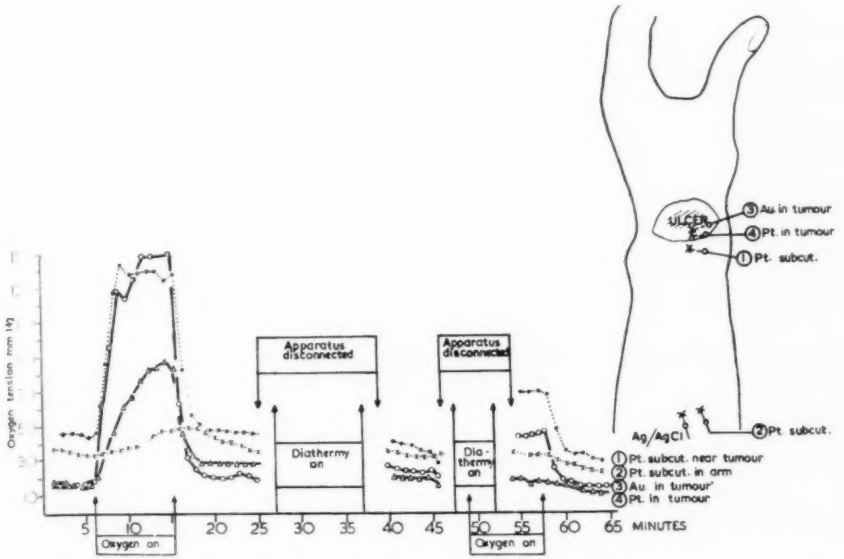


Fig. 9. Case 9. Effect of short-wave diathermy on the oxygen tension in a squamous cell carcinoma.

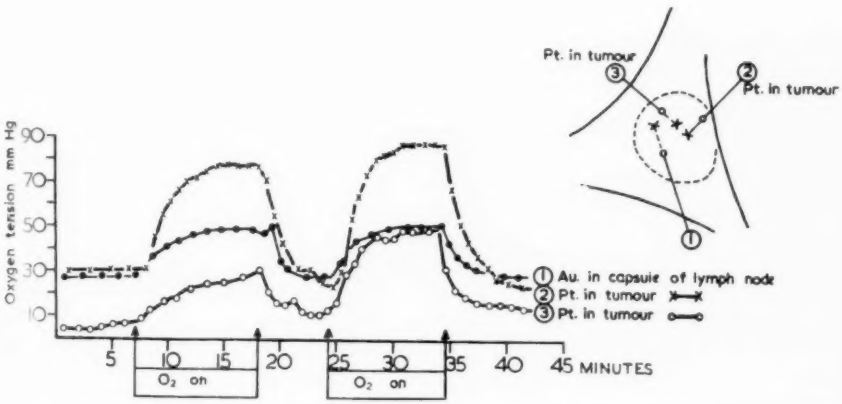


Fig. 10. Case 10. Reticulosis of lymph node in neck, oxygen tension record before treatment.

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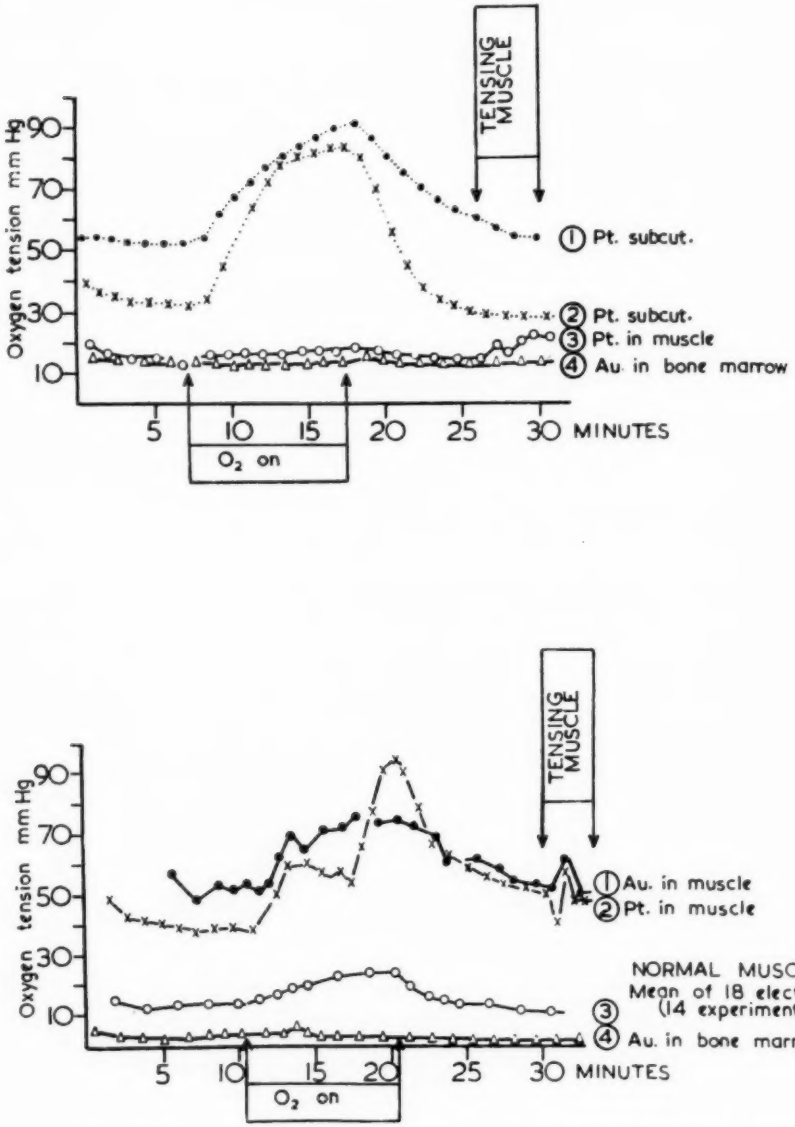

Fig. 11. Case 11. Oxygen tension in muscle, subcutaneous tissue and bone marrow of a normal male aged 25. Lower tracing was taken after the subject had consumed a moderate quantity of alcohol.

Normal tissues

Case 11 (Fig. 11). Mr. P. H. D., aged 25, a normal male. Two separate investigations were carried out on this subject. The upper chart shows a low oxygen tension in muscle and bone marrow with higher readings in subcutaneous tissue. These latter showed a rise when oxygen was breathed. There was a slight increase in oxygen tension in muscle when it was tensed.

The lower chart was made when the subject had just returned from a wedding party at which he had consumed a moderate quantity of alcohol. The bone marrow oxygen tension was still low but in the resting muscle the oxygen tension was high and rose when oxygen was breathed. A mean record of muscle oxygen tension from 18 electrodes in other subjects is superimposed on the lower chart for comparison. It appears that the alcohol caused a considerable vasodilatation in the muscle. The bone marrow records are typical of normal subjects. They show low tensions with negligible alterations when oxygen was breathed.

When investigations on patients were first started oxygen was administered at 5 l/min but it was soon noted that increasing the flow to 7 or 8 l/min consistently increased oxygen tension in tumour tissue.

Discussion

The reliability of the method. The use of the flush-ended type of electrode for the measurement of oxygen tension in tissues by the oxygen-cathode technique has been criticized by CONNELLY (1957), on the grounds of (1) movement artefact, (2) the 'poisoning' of the electrode, (3) that the electrode consumes oxygen, (4) that the current depends on the coefficient of diffusion for oxygen in the tissues.

1. In our experience movement artefact is seldom seen. Readings in tumour are usually very steady — the unsteady readings found with muscle are probably not movement artefacts, but are likely to be due to the changes of activity in muscle which are immediately reflected in circulatory changes and therefore of the oxygen tension in the muscle. Coating the end of the electrode with a thin film of collodion will abolish movement artefact, and SILVER (1959) using this type of electrode in the aorta of foetal sheep found no sign of flow artefact.

2. A glance at the recordings in the patients shows that there is no obvious sign of 'poisoning' of the electrodes to be seen during the hour or so of the experiment. In animals electrodes showed no poisoning in 24 hours. STONER (1958) leaves collodion-coated electrodes in muscle, liver and brain of rats for a week without any sign that the electrodes are becoming less sensitive. In calibration experiments (CATER, SILVER and WILSON 1959) it was found that glutathione, or ammonium sulphide altered the readings by complexing with the electrodes, but there is no reason to suppose that these are normally present in the extracellular spaces in tumour or normal tissues.

3. The recessed electrode (DAVIES and BRINK 1942) does not use oxygen from the tissues during the time of the observation, the reading is also not affected by the coefficient of diffusion of oxygen in the tissues. These are great theoretical advantages, but unfortunately the recessed-electrode is difficult to make and to use. In addition, the response to changes of oxygen-tension is very slow, and an equilibration-interval of 10 to 20 minutes must be left between readings. On the other hand the flush-ended electrode is easy to make and to use; it responds immediately to changes of oxygen tension. Calculation shows that an electrode of 315 μ diameter probably uses less than 1.5 % of the oxygen used by the volume of tissue with which it is in equilibrium, and, in any case, it is also using oxygen under calibration conditions. In metabolically active tissue like tumour its oxygen consumption is probably negligible compared with the tissue.

4. An attempt to investigate whether differences of the diffusion coefficient for oxygen in the tissues and in the calibration fluid, introduce a serious error when flush-ended electrodes are used for quantitative measurements of oxygen tension in vivo was made by CATER, SILVER and WILSON (1959) by perfusing rats' legs with the calibration fluid at 0 to 2° C. It was found that the low temperature and 0.001 M NaCN did not stop completely the utilization of oxygen by the tissues. However, rapid perfusion led to readings on some electrodes inserted into the tissues equal to their calibration values in the perfusion fluid. No difference could be found between the values of oxygen tension given by flush-ended and recessed electrodes in these experiments. Therefore, it was concluded that the extrapolation from the calibration conditions to the in vivo conditions was justified. These experiments suggested that the calibration values obtained by MONTGOMERY and HORWITZ (1950) with the electrode tip embedded in skin were probably too low.

Assessment of results. The size (315 μ diameter) of the flush-ended electrodes used in these studies was deliberately chosen to give a mean sample of the oxygen tension in the tissues. An electrode of this size must lie in extracellular fluid and would receive oxygen from more than one capillary bed. Even so the logarithmic distribution of the results suggests that there is a position effect, i. e. the nearer the electrode lies to the arteriolar-end of a capillary the closer does the oxygen tension approach a maximum value. The use of several electrodes was also designed to obtain 'a fair sample' of the oxygen tension in a tumour. The value of oxygen inhalation as a radiosensitizer is thought to depend on raising the relatively anoxic portions of a tumour from low to maximum sensitivity. Our recent experience with micro-electrodes (10 μ in diameter) suggests that it will be possible to plot the variation of oxygen tension

w h position as the electrode is advanced a few microns at a time through a umour. Such an investigation is planned and it is hoped that it will y ld much needed additional information to the work described here.

When the reading for each electrode after the patient had breathed o gen for 10 minutes was compared with the reading obtained when a was breathed, the ratio was found to be a constant of about 2.3 f normal muscle, subcutaneous tissue, tumour before radiotherapy, a l for tissues near tumour both before and after radiotherapy. This r io was significantly increased to 2.9 in tumours examined a day or s after completion of a course of radiotherapy. (In some cases the r liotherapy was for radical cure, in others for palliation only.) In most c es there were obvious signs of a radiation reaction with erythema of t e skin over the irradiated area, but if the augmented response to b eathing oxygen was merely due to vasodilatation it would have been g ven by electrodes inserted into tissues near tumour which were also i the irradiated area. The findings, therefore, suggest that damage t the rapidly metabolising tumour cells was the reason for this change. The average level of oxygen tension in tumour when air was breathed was higher after radiotherapy than before treatment. This difference was even more marked when oxygen was breathed. Our findings suggest that if a tumour has a low oxygen tension then inhalation of oxygen at atmospheric pressure will be beneficial in radiotherapy. The rapidly growing, oedematous, cyanosed tumour shown in Fig. 4 gave an excellent therapeutic response to oxygen inhalation and radiotherapy. The oxygen tension in the tumour before radiotherapy was very low and there appeared to be little response to the inhalation of oxygen. During the first two or three daily treatments little benefit would be expected, but when the tumour cells were damaged, and the inflammatory phase of the radiation reaction had begun, then breathing oxygen would be expected to increase the oxygen tension just where it mattered most, namely in those parts of the tumour that had a low oxygen tension and might therefore be relatively radio-resistant. Controlling infection in an ulcerated growth by antibiotics and thus reducing the oedema may also have an important effect on oxygen tension and radiosensitivity.

The experiments with short-wave diathermy were performed with the idea of increasing the vasodilatation and circulation through tissues by heat. However, the results (Fig. 9) indicated a lower oxygen tension and a decreased response to oxygen inhalation after diathermy. The variable which affects the oxygen tension in tissues most markedly is the rate of metabolism (KETY 1957). It is therefore likely that the fall in oxygen tension after diathermy was due to the raised temperature increasing the metabolic rate of the tissues. In keeping with this explanation was our finding of a very low oxygen tension in an anaesthetised

rat dying of hyperthermia due to heat applied externally. The experiments with short-wave diathermy presented great technical difficulties and indeed it would not be easy to use diathermy combined with radiotherapy as a practical form of treatment; so perhaps it is fortunate that this idea did not yield the hoped-for answer. On the other hand it is worth reporting in case others should consider using diathermy and roentgen as a combined therapy. These experiments of course do not exclude the value of diathermy as an agent for destroying cancer cells by heat.

Oxygen inhalation and injections of Synkavit. The experiments with Synkavit were performed because a clinical trial of combined treatment with oxygen inhaled at atmospheric pressure, intravenous injection of Synkavit, and radiotherapy has been in progress at the Radiotherapeutic Centre in Cambridge since 1953 (MITCHELL 1957a, b, 1959). There was the possibility that intravenous Synkavit, which MITCHELL (1953, 1954, 1959) has shown tends to localize in tumour cells, would alter the oxygen tension in the tumour. These patients were given oxygen to breathe and when the oxygen tension appeared to be maximal, as judged from minute to minute readings on the electrodes, Synkavit was injected intravenously. The administration of oxygen was continued for half an hour. It was found that the levels of oxygen tension slowly increased and there was no suggestion that Synkavit lowered the oxygen tension. Therefore, it is hoped that both oxygen inhalation and Synkavit will exert their specific radiosensitizing effects. These experiments are interesting because they follow closely the conditions when oxygen is used in clinical radiotherapy. (Our test of oxygen inhalation for 10 minutes was chosen for convenience.) In the clinic, Synkavit is injected 30 minutes before radiotherapy and oxygen is commenced 20 minutes before and continued throughout radiotherapy so that it is usually breathed for periods of 30 to 40 minutes.

Practical considerations. In the course of this investigation certain practical points emerged. The rate of flow of oxygen to the mask should be 7 or 8 l/min as this rate of flow was found to give a higher oxygen tension than when the flow was 5 l/min.

The importance of muscular relaxation during radiotherapy was emphasised by the marked increase of oxygen tension which occurred when a muscle was tensed. It would appear that ingestion of alcohol increased the oxygen tension in muscle, presumably by vasodilatation. It was noted in certain cases of anaemia that inhalation of oxygen caused a very big increase in the oxygen tension of muscle and subcutaneous tissue. The levels in these patients when breathing air were rather low. These findings agree with what would be expected from the physiology

o the anaemic condition with a low capacity of the blood for the carriage o oxygen and a high rate of circulation through the tissues. The im- p tance of correcting anaemia if possible before treatment has long been r lised.

Administration of oxygen at atmospheric pressure to patients is a s ple, safe and comfortable technique. Its effectiveness as a radio- s sitizer can only be judged when the results of clinical trials become a ilable. It will then be possible to compare the usefulness of oxygen l athed at atmospheric pressure with oxygen breathed at high pressures. l . Churchill-Davidson kindly showed us the preliminary results o tained by radiotherapy of patients under 3 atmospheres pressure of o ygen. This technique would appear to have given very good results w th sarcomas of bone and cartilage, but to have resulted in a rather h gh proportion of necrosis of cartilage during the treatment of laryngeal c rcinoma. It is possible in relatively anoxic tissues such as bone and c rtilage that high pressure oxygen may be an advantage, but for most t mours oxygen at atmospheric pressure would appear to be quite satis- factory. The opposite approach is to try and render the tissues anoxic so that tumour and normal tissues alike are reduced to a common low level of radiosensitivity. This anoxia technique advocated by Wright (1958) would appear to be difficult and dangerous in patients, while easy and practical in the mouse. The anoxic technique may be practical if combined with hypothermia. Cater and Weiss (1959) demonstrated that cooling mice to 1° C resulted in low oxygen tensions in spleen, testis and bone marrow and Weiss (1959) has discussed the application of these findings to practical radiotherapy.

Acknowledgements

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SUMMARY

Quantitative measurements of oxygen tension in tumours and normal tissues of patients were made by the oxygen cathode technique before and after radiotherapy. Statistical analysis showed that log oxygen tension has a normal distribution. The ratio,

$\frac{\text{tissue oxygen tension when breathing oxygen}}{\text{tissue oxygen tension when breathing air}} = K$, a constant of mean value 2.1 to 3 for muscle, subcutaneous tissue, tissues near tumour, and tumour before treatme . After radiotherapy, K is significantly higher for tumour (2.93), but for no other tiss . The effect of the radiosensitizer Synkavit on the oxygen tension is described. Warm g by diathermy reduced tumour oxygen tension and the response to breathing oxyg . The findings encourage use of oxygen inhaled at atmospheric pressure as a radiosensiti r, but patients require 7 to 8 l/min for 30 min, to obtain maximum tumour oxygen t n-sion.

ZUSAMMENFASSUNG

Quantitative Messungen der Sauerstoffspannung in Tumoren und in norma n Geweben von Patienten wurden mit der Sauerstoffkathodentechnik vor und nach er Strahlenbehandlung ausgeführt. Statistische Analysen zeigten, dass der Logarith us der Sauerstoffspannung eine normale Verteilung hat. Das Verhältnis $\frac{\text{Gewebssauerstoffspannung bei Sauerstoffeinatmung}}{\text{Gewebssauerstoffspannung bei Lufteinatmung}} = K$ zeigt vor der Behandl ng einen konstanten Mittelwert von 2.1 bis 2.3 für Muskulatur, subkutanes Gewe e, tumornahes Gewebe und Tumorgewebe. Nach der Bestrahlung ist K signifikant hö er für Tumorgewebe (2.93), aber für kein anderes Gewebe. Die Wirkung des Strahlensensibilisators Synkavit auf die Sauerstoffspannung wird beschrieben. Erwärmung durch Diathermie reduzierte die Sauerstoffspannung und die Reaktion auf Sauerstoffeinatmung. Die Befunde ermutigen dazu, den bei atmosphärischem Druck eingeatmeten Sauerstoff als Strahlensensibilisator zu benutzen. Die Patienten müssen jedoch 30 Minuten lang 7—8 l Sauerstoff per Minute einatmen, um maximale Sauerstoffspannung im Tumorgewebe zu erzielen.

RÉSUMÉ

Les auteurs ont effectué des mesures quantitatives de tension d'oxygène par la technique de la cathode d'oxygène sur des tumeurs et des tissus normaux de malades avant et après radiothérapie. L'analyse statistique a montré que le logarithme de la tension d'oxygène a une distribution normale. Le rapport

$$\frac{\text{tension d'oxygène tissulaire sous inhalation d'oxygène}}{\text{tension d'oxygène tissulaire sous inhalation d'air}} = K$$

est une constante dont la valeur moyenne est de 2.1 à 2.3 pour le muscle, le tissu sous-cutané, les tissus péritumoraux et la tumeur avant le traitement. Après la radiothérapie. K est significativement plus élevé pour la tumeur (2.93), mais ne l'est pour aucun autre tissu. Les auteurs décrivent l'effet du radiosensibilisateur Synkavit sur la tension d'oxygène. Le réchauffement par la diathermie réduit la tension d'oxygène de la tumeur et la réponse à l'inhalation d'oxygène. Ces résultats sont en faveur de l'emploi de l'oxygène inhalé à la pression atmosphérique comme radiosensibilisateur, mais il faut en administrer aux malades 7 à 8 l/min pendant 30 minutes pour obtenir une tension d'oxygène tumorale maximale.

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